Appendix A. Medications Used Off-label for Fibromyalgia Syndrome in the U.S.

Trade Name	Generic Name	Manufacturer	Therapeutic Class	FDA-Fibro	Subclass
Prozac	Fluoxetine	Eli Lilly and Co	Antidepressants	Off label	SNRI
Elavil	Amitriptyline	AstraZeneca	Antidepressants	Off label	Tricyclic anti-depressant
Paxil CR	Paroxetine	GlaxoSmithKline	Antidepressants	Off label	SNRI
Mirapex	Pramepixole	Boehringer Ingelheim	Anti-Dyskinetic	Off label	Nonergot Dopamine Agonist
Amrix	Cyclobenzapine	Cephalon, Inc	Muscle relaxant	Off label	Centally-acting skeletal muscle relaxant
Ultracet	Tramadol	Janssen Pharmaceuticals	Analgesic	Off label	Synthetic opioid analgesic, SNRI
Ultram	Tramadol	Janssen Pharmaceuticals	Analgesic	Approved for chronic pain	Synthetic opioid analgesic, SNRI
ConZip	Tramadol	Vertical Pharmaceuticals	Analgesic	Off label	Synthetic opioid analgesic, SNRI
Neurontin	Gabapentin	Pfizer	Anti-convulsant	Off label	GABA (gamma amino-butyric acid) analog
Deptran	Doxepin	Generic	Antidepressant, Anxiolytic, Antipruritic	Off label	Tricyclic antidepressant
Tizanadine	Xanaflex	Cephalon, Inc	Muscle relaxant	Off label	Central alpha-2 Adrenergic Agonist
Flexeril	Cyclobenzapine	McNeil Consumer and Specialty	Muscle relaxant	Off label	Centrally-acting skeletal muscle relaxant
Ambien	Zolpidem	Sanofi Aventis	Sedative-Hypnotic(Non-Barbiturate)	Off label	Imidazopyridine
Lunesta	Eszipoclone	Sunovion Pharms Inc	Non-barbiturate hypnotic	Off label	Non-benzodoazepine
Klonopin	Clonazepam	Roche	Anxiolytic	Off label	Benzodiazepine
Lexapro	Escitalopram	Forest Labs	Antidepressants	Off label	SSRI
Zoloft	Sertraline	Pfizer	Antidepressants	Off label	SSRI
Motrin	Ibuprofen	Pfizer	Analgesic/Anti-inflammatory	Off label	NSAID
Advil	Ibuprofen	Pfizer	Analgesic/Anti-inflammatory	Off label	NSAID
Aleve	Naproxen	Bayer	Analgesic/Anti-inflammatory	Off label	NSAID
Celebrex	Celecoxib	Pfizer	Analgesic/Anti-inflammatory	Off label	NSAID
Aspirin	Acetylsalicyclic acid	Bayer	Analgesic/Anti-inflammatory	Off label	NSAID
Tylenol	Acetaminophen	McNeil Consumer Healthcare	Analgesics	Off label	Non-opioid Analgesics
Desyrel	Trazadone	Generic	Antidepressants	Off label	serotonin antagonist reuptake inhibitor
Oxycontin	Oxycodone	Purdue	Analgesics	Off label	Opioid Analgesics
Percocet	Oxycodone	Endo	Analgesics	Off label	Opioid Analgesics
Vicodin	Hydrocodone	AbbVie	Analgesics	Off label	Opioid Analgesics
Dilaudid	Hydromorphine	Purdue	Analgesics	Off label	Opioid Analgesics
MsContin	Morphine	Purdue	Analgesics	Off label	Opioid Analgesics
Duragesic	Fentanyl	Generic	Analgesics	Off label	Opioid Analgesics
Valium	Diazepam	Roche	Anxiolytic	Off label	Benzodiazepine
Clinoxan	Tetrazapem	Generic	Anxiolytic	Off label	Benzodiazepine
Millipred	Prednisolone	Generic	Antiinflammatory-Immunosuppressant	Off label	Corticosteroid, Glucocorticosteroid
Xyrem	Sodium Oxybate	Jazz Pharmaceuticals	CNS depressant	Off label	Narcotic sedative: FDA rejected for FM

Abbreviations: **FDA**-Food and Drug Administration; **FM**-Fibromyalgia; **NSAID**-Non-Steroidal Anti-Inflammatory Drugs; **SNRI**-Serotonin Norepinephrine Re-uptake Inhibitors; **SSRI**-Selective Serotonin Reuptake Inhibitors

Appendix B: Fibromyalgia Search Strings

Database: Ovid MEDLINE(R) <1946 to November Week 2 2013> Search Strategy:

---

1 meta analysis as topic/ (14174)
2 meta-analy$.tw. (58094)
3 metaanaly$.tw. (1283)
4 meta-analysis/ (51865)
5 (systematic adj (review$1 or overview$1)).tw. (47251)
6 exp Review Literature as Topic/ (7718)
7 or/1-6 (115989)
8 cochrane.ab. (33481)
9 embase.ab. (29939)
10 (psychlit or psyclit).ab. (1190)
11 (psychinfor or psycinfo).ab. (8325)
12 or/8-11 (48550)
13 reference list$.ab. (11704)
14 bibliograph$.ab. (11806)
15 hand search.ab. (876)
16 relevant journals.ab. (904)
17 manual search$.ab. (2248)
18 or/13-17 (25683)
19 selection criteria.ab. (26165)
20 data extraction.ab. (10119)
21 19 or 20 (33811)
22 review/ (1921415)
23 21 and 22 (26055)
24 comment/ (537610)
25 letter/ (807565)
26 editorial/ (337037)
27 animal/ (5506319)
28 human/ (13689930)
29 27 not (28 and 27) (3970292)
30 or/24-26,29 (5167730)
31 7 or 12 or 18 or 23 (144954)
32 31 not 30 (135948)
33 randomized controlled trials as topic/ (102691)
34 randomized controlled trial/ (390224)
35 random allocation/ (81795)
36 double blind method/ (131905)
37 single blind method/ (19625)
38 clinical trial/ (504861)
39 clinical trial, phase i.pt. (16220)
40 clinical trial, phase ii.pt. (26918)
41 clinical trial, phase iii.pt. (10181)
42 clinical trial, phase iv.pt. (997)

43 controlled clinical trial.pt. (89925)
44 randomized controlled trial.pt. (390224)
45 multicenter study.pt. (182851)
46 clinical trial.pt. (504861)
47 exp Clinical trials as topic/ (296596)
48 or/33-46 (959756)
49 (clinical adj trial$).tw. (211765)
50 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (129589)
51 placebos/ (33783)
52 placebo$.tw. (161799)
53 randomly allocated.tw. (16078)
54 (allocated adj2 random$).tw. (18581)
55 49 or 50 or 51 or 52 or 53 or 54 (418203)
56 48 or 55 (1126654)
57 case report.tw. (184302)
58 case report.tw. (184302)
59 letter/ (807565)
60 historical article/ (300466)
61 57 or 58 or 59 or 60 (1281048)
62 56 not 61 (1102751)
63 exp cohort studies/ (1371088)
64 cohort$.tw. (263920)
65 controlled clinical trial.pt. (89925)
66 epidemiologic methods/ (30994)
67 limit 66 to yr=1971-1983 (5365)
68 63 or 64 or 65 or 67 (1546297)
69 exp case-control study/ (666622)
70 (case$ and control$).tw. (314550)
71 69 or 70 (892406)
72 exp Fibromyalgia/ (6360)
73 fibromyalgia.ti,ab. (6304)
74 myofascial pain syndrome*.ti,ab. (387)
75 32 or 62 or 68 or 71 (2692964)
76 72 or 73 or 74 (7791)
77 75 and 76 (2584)
78 limit 77 to "all adult (19 plus years)" (1910)
79 limit 78 to "all child (0 to 18 years)" (309)
80 77 not 79 (2275)
81 78 or 80 (2584)

Database: Embase Classic+Embase <1947 to 2014 Week 06>Search Strategy:

---

1 fibromyalgia/ (13099)
2 fibromyalgia.ti,ab. (10216)
3 exp myofascial pain/ (6786)
4 myofacial pain syndrome*.ti,ab. (27)
5 1 or 2 or 3 or 4 (20091)
6 retracted article/ (7252)
7 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab. (1017703)
8 (animal$ not human$).sh,hw. (3953097)
9 (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/ (4100517)
10 6 or 7 (1024797)
11 10 not (8 or 9) (836009)
12 exp cohort analysis/ (170749)
13 exp longitudinal study/ (69111)
14 exp prospective study/ (264902)
15 exp follow up/ (816417)
16 cohort$.tw. (389844)
17 12 or 13 or 14 or 15 or 16 (1380858)
18 exp case-control study/ (94713)
19 (case$ and control$).tw. (472185)
20 18 or 19 (507755)
21 (case$ and series).tw. (193606)
22 exp review/ (2091689)
23 (literature adj3 review$).ti,ab. (234902)
24 exp meta analysis/ (80432)
25 exp "Systematic Review"/ (70130)
26 22 or 23 or 24 or 25 (2301941)
27 (medline or embase or pubmed or cinahl or amed or psychlit or psychinfo or scisearch or cochrane).ti,ab. (106533)
28 retracted article/ (7252)
29 27 or 28 (113736)
30 26 and 29 (84397)
31 (systematic$ adj2 (review$ or overview)).ti,ab. (72028)
32 (meta?anal$ or meta anal$ or metaanal$ or metanal$).ti,ab. (80995)
33 30 or 31 or 32 (170495)
34 11 or 17 or 20 or 21 or 33 (2715453)
35 5 and 34 (4204)
36 limit 35 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) (379)
37 limit 36 to (adult <18 to 64 years> or aged <65+ years>) (289)
38 35 not 36 (3825)
39 37 or 38 (4114)
40 limit 39 to (book or book series or conference abstract or conference paper or conference proceeding or "conference review" or editorial or letter or note or report or short survey or trade journal) (887)
41 39 not 40 (3227)

Database: PsycINFO <1806 to January Week 3 2014> Search Strategy:

---

1 fibromyalgia/ (1194)
2 myofacial pain syndrome*.ti,ab. (2)
3 fibromyalgia.ti. (1331)
4 1 or 2 or 3 (1594)
5 limit 4 to ("0200 book" or "0240 authored book" or "0280 edited book" or "0300 encyclopedia" or "0400 dissertation abstract") (168)
6 4 not 5 (1426)
7 limit 6 to (abstract collection or bibliography or chapter or "column/opinion" or "comment/reply" or dissertation or editorial or encyclopedia entry or letter or obituary or poetry or publication information or reprint or review-book or review-media or review-software & other) (126)
8 6 not 7 (1300)
9 limit 8 to (childhood <birth to 12 years> or adolescence <13 to 17 years>) (34)
10 limit 9 to adulthood <18+ years> (23)
11 8 not 9 (1266)
12 10 or 11 (1289)

Database: Cochrane Library Search Strategy:

Fibromyalgia' in title, abstract, keyword

AMED (Allied and Complementary Medicine) <1985 to February 2014>

Set	Search
001	meta analysis.af.
002	meta-analy$.tw.
003	metaanaly$.tw.
004	meta-analysis/
005	(systematic adj (review$1 or overview$1)).tw.
006	literature review.af.
007	1 or 2 or 3 or 4 or 5 or 6
008	cochrane.ab.
009	embase.ab.
010	(psychlit or psyclit).ab.
011	(psychinfor or psycinfo).ab.
012	8 or 9 or 10 or 11
013	reference list$.ab.
014	bibliograph$.ab.
015	hand search.ab.
016	relevant journals.ab.
017	manual search$.ab.
018	13 or 14 or 15 or 16 or 17
019	selection criteria.ab.
020	data extraction.ab.
021	19 or 20
022	review.af.
023	21 and 22
024	letter.pt.
025	comment.pt.
026	editorial.pt.
027	animal.af.
028	human.af.
029	(animal not (human and animal)).af.
030	24 or 25 or 26 or 29
031	7 or 12 or 18 or 23
032	((meta analysis or meta-analy$ or metaanaly$ or meta-analysis or (systematic adj (review$1 or overview$1)) or literature review or (cochrane or embase or (psychlit or psyclit) or (psychinfor or psycinfo)) or (reference list$ or bibliograph$ or hand search or relevant journals or manual search$) or ((selection criteria or data extraction) and review)) not (letter or comment or editorial or (animal not (human and animal)))).af.
033	randomized controlled trials/
034	randomized controlled trial/
035	random allocation/
036	double blind method/
037	single blind method/
038	clinical trial/
039	clinical trial.pt.

040 controlled clinical trial.pt.
041 randomized controlled trial.pt.
042 multicenter study.pt.
043 clinical trial.pt.
044 clinical trial.af.
045 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
046 (clinical adj trial$).tw.
047 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$ 3)).tw.
048 placebos/
049 placebo$.tw.
050 randomly allocated.tw.
051 (allocated adj2 random$).tw.
052 46 or 47 or 48 or 49 or 50 or 51
053 45 or 52
054 case report.tw.
055 case report.tw.
056 letter.pt.
057 historical article.af.
058 54 or 56 or 57
059 53 not 58
060 exp cohort studies/
061 cohort$.tw.
062 controlled clinical trial.pt.
063 epidemiologic methods/
064 60 or 61 or 62
065 exp Case Control Studies.
066 (case$ and control$).tw.
067 65 or 66
068 exp FIbromyalgia/
069 fibromyalgia.ti,ab.
070 myofascial pain syndrome*.ti,ab
071 32 or 59 or 64 or 67
072 68 or 69 or 70
073 71 and 72
074 adult/ or aged/ or middle aged/
075 child/ or infant/
076 73 and 74
077 76 not 75
078 (adult or aged or middle aged).af
079 (child or infant).af.
080 73 and 78
081 (73 and 78) not 79

Appendix C
Treatments for Fibromyalgia in Adult Subgroups
Risk of Bias Assessment for Observational Studies

Question	Response	Criteria	Justification
		Internal Validity	
1. Study design: prospective, retrospective or mixed?	Prospective ☐	Outcome had not occurred when study was initiated; information was collected over time	
	Mixed ☐	One group was studied prospectively; other(s) retrospectively	
	Retrospective ☐	Analyzed data from past records, claims	
2. Were inclusion/exclusion criteria clearly stated?	Yes ☐	Clearly stated	
	Partially ☐	Some, but not all criteria stated or some not clearly stated.	
	No ☐	Unclear	
3. Were baseline characteristics measured using valid and reliable measures and are they equivalent in both groups?	Yes ☐	Valid measures, groups ~equivalent	
	No ☐	Non-validated measures or nonequivalent groups	
	Uncertain ☐	Could not be ascertained	
4. Were important variables known to impact the outcome(s) assessed at baseline?	Yes ☐	Yes, most or all known factors were assessed	
	No ☐	Critical factors are missing	
	Uncertain ☐		
5. Is the level of detail describing the intervention adequate?	Yes ☐	Intervention sufficiently described	
	Partially ☐	Some of the above features.	
	No ☐	Intervention poorly described	
6. Is the selection of the comparison group appropriate?	Yes ☐	Other fibromyalgia patients with similar patient characteristics, severity and comorbid features	
7. Was the impact of a concurrent intervention or an unintended exposure that might bias results isolated?	Yes ☐	By inclusion criteria, protocol or other means	
	Partially ☐	Some were isolated, others were not	
	No ☐	Important concurrent interventions were not isolated or prohibited	
8. Were there attempts to balance the allocation across groups? (e.g., stratification, matching or propensity scores)	Yes ☐	(*If yes, what method was used?)*	
	No ☐		
	Uncertain ☐	Could not be ascertained	
9. Were outcomes assessors blinded?	Yes ☐	Who assessed outcomes?	
	No ☐		
	Uncertain ☐	Not reported	
10. Were outcomes assessed using valid and reliable measures, and used consistently across all study participants?	Yes ☐	Measures were valid and reliable (i.e., objective measure, validated scale/tool); consistent across groups	
	Partially ☐	Some of the above features	
	No ☐	None of the above features	
	Uncertain ☐	Could not be ascertained.	
11. Was length of followup the same for all groups?	Yes ☐		
	No ☐		
	Uncertain ☐	Could not be ascertained	

Question	Response	Criteria	Justification
	Internal Validity		
12. Did attrition result in differences in group characteristics between baseline and followup?	Yes ☐	*(If yes, for which followup period(s)?)*	
	No ☐		
	Uncertain ☐	Could not be ascertained	
13. If dissimilar baseline characteristics, does the analysis control for baseline differences between groups?	Yes ☐	What method?	
	No ☐		
	Uncertain ☐	Could not be ascertained	
14. Were confounding and/or effect modifying variables assessed using valid and reliable measures across all study participants?	Yes ☐		
	No ☐		
	Uncertain ☐	Could not be ascertained (i.e., retrospective designs where eligible at baseline could not be determined)	
	NA ☐	No confounders or effect modifiers included in the study.	
15. Were important confounding and effect modifying variables taken into account in design and/or analysis? (e.g., matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment)	Yes ☐		
	Partially ☐	Some variables taken into account or adjustment achieved to some extent.	
	No ☐	Not accounted for or not identified.	
	Uncertain ☐	Could not be ascertained	
16. Are statistical methods used to assess the primary outcome appropriate to the data?	Yes ☐	Statistical techniques used must be appropriate to the data.	
	Partially ☐		
	No ☐		
	Uncertain ☐	Could not be ascertained	
17. Is there suggestion of selective outcome reporting?	Yes ☐		
	No ☐	Not all prespecified outcomes reported, subscales not prespecified reported, outcomes reported incompletely	
	Uncertain ☐	Could not be ascertained	
18. Was the funding source identified?	No ☐		
	Yes ☐	Who provided funding?	
	Uncertain ☐		

Additional subgroup items[1]	
Was subgroup variable measured at baseline?	
Were subgroups pre-specified (a priori)?	
Was direction of subgroup effect on each/main outcome specified a priori? If so, was result consistent with it?	
Is subgroup effect significant? Skeptical p>0.01; Maybe (0.01<p<0.1) vs p<0.001 believable)	
Is subgroup effect large?	
Is subgroup effect independent? (is another interaction significant that is a related variable?)	
Is the interaction effect consistent across similar outcomes in the study?	

Question	Response	Criteria	Justification
	Internal Validity		
Overall Assessment			
Overall Risk of Bias assessment	Low ☐	Results are believable taking study limitations into consideration	
	Moderate ☐	Results are probably believable taking	

Question	Response	Criteria	Justification
		Internal Validity	
		study limitations into consideration	
	High ☐	Results are uncertain taking study limitations into consideration	

Reference:

1. Sun X, Briel M, Walter SD, et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ. 2010;340:c117. PMID 2035401

RCT Risk of bias assessment: Fibromyalgia subgroup studies

Selection Bias	
Was method of randomization used to generate the sequence described in sufficient detail to assess whether it should produce comparable groups? (inadequate randomization?)	
Were all randomized participants analyzed in the group to which they were allocated?	
Were the groups similar at baseline regarding the most important prognostic indicators?	
Was method of treatment allocation adequate to keep treatment concealed until desired time?(inadequate allocation concealment)	
Risk of selection bias (inadequate randomization or allocation concealment):	**[Low, Unclear, High]**
Performance Bias	
Was the care provider blinded to the intervention?	Yes, no, NR
Were the participants blinded to the intervention?	Yes, no, NR
Nondrug interventions: Were interventions adequately defined so they could be replicated?	
Was the intended blinding effective?	
Risk of performance bias due to lack of participant and personnel blinding, intervention definition & fidelity to treatment?	**[Low, Unclear, High]**
Detection Bias	
Were the outcome assessors blinded to the intervention?	Yes, no, NR, NA
Was the scale/tool used to measure outcomes validated, reliable?	
Were co-interventions avoided?	
Was the timing of the outcome assessment similar in all groups?	
Were significance estimates for results appropriately corrected for multiple comparisons?	
Was study adequately powered – To detect main effects? To detect differences in subgroups?	
Risk of detection bias due to lack of outcome assessor blinding, measurement of outcomes, statistical analysis, low study power	**[Low, Unclear, High]**
Attrition Bias	
Was attrition lower than 20%? -overall -in subgroups	Y, N, NR, NR for SG %
Were reasons for incomplete/missing data adequately explained? (# assessed, # dropped out, # lost to follow-up)	
Were losses to followup also reported for subgroups?	
Was incomplete data handled appropriately?	
Risk of attrition bias due to amount, nature, or handling of incomplete outcome data?	**[Low, Unclear, High]**
Reporting Bias	
Were all outcomes reported in Results or were only select outcomes reported ?	
Were results (in tables and/or text) reported for all randomized patients -for main outcomes? -for all outcomes? -for subgroups?	
What is the risk of reporting bias due to selective outcome reporting?	**[Low, Unclear, High]**

Other Sources of Bias	
Are there other risks of bias? If yes, describe them	
Additional subgroup items	
Was subgroup variable measured at baseline or after randomization?	
Were subgroups pre-specified (a priori)?	
Was direction of subgroup effect on each/main outcome specified a priori? If so, was result consistent with it?	
Is subgroup effect significant? (skeptical: p>0.01 vs maybe (0.01<p<0.1) vs p<0.001 believable)	S-M-B vs NR -or text of "NS"
Is subgroup effect large?	
Is subgroup effect independent?	
Is the interaction effect consistent across similar outcomes in the study?	
Overall Risk of Bias Assessment by outcome(s)	**[Low, Moderate or High] and explanation (1-2 sentences)**

References:

1. Sun X, Briel M, Walter SD, et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ. 2010;340:c117. PMID 2035401
2. Viswanathan M, Ansari M, Berkman N, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. AHRQ. 2012.
3. Higgins JPT, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions: Version 5.1.0. The Cochrane Collaboration; 2011.

Pooled individual patient data RCTs risk of bias assessment: Fibromyalgia subgroup studies

Study Inputs	
Overall risk of bias summary – input study #1	
Overall risk of bias summary – input study #2	
Overall risk of bias summary – input study #3	
Overall risk of bias summary – input study #4	
Considerations for subgroup interaction in IPD pooled RCT analysis	
Did authors consider inclusion of "across-trial" information? [Fisher, 2011 #4632]	
Analytic technique selected, ordered from most to least optimal:[Fisher, 2011 #4632] 1. OSM: "one-stage" model with covariate interaction (do authors include a term for trial membership, if this method was chosen?) 2. PWT: pooling of within-trial covariate interaction 3. CWA: "manually" combining separately calculated within- and across-trial effects 4. TCDS: testing for treatment effect differences across covariate subgroups	
Was heterogeneity in interaction effects discussed? (E.g., large I^2 or obvious outlier, or confounding)	
Optimal presentation: were results of interaction effect presented graphically for reader to see (similar to "default presentation style" suggested by Fisher 2011[Fisher, 2011 #4632])?	
Risk of analytic bias based on IPD method for pooled analysis:	[Low, Unclear, High]
Reporting Bias- pooled IPD analysis	
Were all outcomes reported in Results or were only select outcomes reported? (compare to methods section)	
Were results (in tables and/or text) reported for all randomized patients -for main outcomes? -for all outcomes? -for subgroups?	
What is the risk of reporting bias due to selective outcome reporting in pooled analysis?	[Low, Unclear, High]
Additional subgroup items- pooled IPD analysis (adapted from Sun et al.[Sun, 2010 #4677])	
Were subgroups pre-specified (a priori in RCTs) or only for pooled analysis?	
Was direction of subgroup effect on each/main outcome specified a priori? If so, was result consistent with it?	
Is subgroup effect significant? (Skeptical: p>0.01 vs Maybe (0.01<p<0.1) vs p<0.001 Believable)	S-M-B vs NR -or text of "NS"
Is subgroup effect large?	
Is subgroup effect independent? (is another interaction significant for a related variable?)	
Is the interaction effect consistent across similar outcomes in the study?	
Risk of Bias Assessment for pooled IPD methods and reporting	[Low, Moderate or High] and brief rationale (transfer to bottom of this assessment form)
RCT inputs for pooled analysis	
Selection Bias-input RCTs	
Was method of randomization used to generate the sequence described in sufficient detail to assess whether it should produce comparable groups? (inadequate randomization)?	
Were all randomized participants analyzed in the group	

to which they were allocated? (Intention to treat (ITT))	
Were the groups similar at baseline regarding the most important prognostic indicators?	
Was method of treatment allocation adequate to keep treatment concealed until desired time?(inadequate allocation concealment)	
Risk of selection bias (inadequate randomization or allocation concealment):	[Low, Unclear, High]
Performance Bias-input RCTs	
Was the care provider blinded to the intervention?	Yes, no, NR
Were the participants blinded to the intervention?	Yes, no, NR
Nondrug interventions: Were interventions adequately defined so they could be replicated?	
Was the intended blinding effective?	
Risk of performance bias due to lack of participant and personnel blinding, intervention definition & fidelity to treatment?	[Low, Unclear, High]
Detection Bias-input RCTs	
Were the outcome assessors blinded to the intervention?	Yes, no, NR, NA
Was the scale/tool used to measure outcomes validated, reliable?	
Were co-interventions avoided?	
Was the timing of the outcome assessment similar in all groups?	
Were significance estimates for results appropriately corrected for multiple comparisons?	
Was study adequately powered – To detect main effects? To detect differences in subgroups?	
Risk of detection bias due to lack of outcome assessor blinding, measurement of outcomes, statistical analysis, low study power	[Low, Unclear, High]
Attrition Bias-input RCTs	
Was attrition lower than 20%? -overall -in subgroups	Y, N, NR, NR for SG %
Were reasons for incomplete/missing data adequately explained? -# assessed, -# dropped out, # lost to follow-up, # died	
Were losses to follow-up also reported for subgroups?	
Incomplete data handled appropriately?	
Risk of attrition bias due to amount, nature, or handling of incomplete outcome data?	[Low, Unclear, High]
Reporting Bias-input RCTs	
Were all outcomes reported in Results or were only select outcomes reported (compared to methods section)?	
Were results (in tables and/or text) reported for all randomized patients (vs. only treatment completers) -for main outcomes? -for all outcomes? -for subgroups?	
What is the risk of reporting bias due to selective outcome reporting?	[Low, Unclear, High]
Other Sources of Bias	
Are there other risks of bias? If yes, describe	
Additional subgroup items-input RCTs	
Was subgroup variable measured at baseline or after randomization?	
Were subgroups pre-specified (a priori)?	

Was direction of subgroup effect on each/main outcome specified a priori? If so, was result consistent with it?	
Is subgroup effect significant? Skeptical: p>0.01 vs Maybe (0.01<p<0.1) vs p<0.001 Believable [Sun, 2010 #4677]	S-M-B vs NR -or text of "NS"
Is subgroup effect large?	
Is subgroup effect independent?	
Is the interaction effect consistent across similar outcomes in the study?	
Risk of Bias Assessment for RCT inputs (by outcome)	[Low, Moderate or High] and explanation (1-2 sentences)
Risk of Bias Assessment for pooled IPD methods and reporting (from above)	[Low, Moderate or High] and explanation (1-2 sentences)
Overall Risk of Bias Assessment (by outcome)	[Low, Moderate or High] and brief explanation

References

1. Higgins JPT, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions: Version 5.1.0: The Cochrane Collaboration; 2011.
2. Viswanathan M, Ansari M, Berkman N, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions: AHRQ. 2012.
3. Sun X, Briel M, Walter SD, et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010; 340:c117. 20354011.
4. Fisher DJ, Copas AJ, Tierney JF, et al. A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners. J Clin Epidemiol 2011; Sep;64(9):949-67. 21411280.

Abbreviations: **CWA**: manually-combining separately calculated within- and across-trial effects; **OSM**: One-stage model with covariate interaction; **PWT**: pooling of within-trial covariate interactions; **RCT**: randomized clinical trial; **TCDS**: Testing for treatment effect differences across covariate subgroups

Appendix D. Excluded Studies (all studies)

No Subgroup (n=20)

1. Huuhka MJ, Haanpaa ML, Leinonen EV. Electroconvulsive therapy in patients with depression and fibromyalgia. European Journal of Pain 2004; Aug;8(4):371-6. 15207518.
2. Jones KD, Sherman CA, Mist SD, et al. A randomized controlled trial of 8-form Tai chi improves symptoms and functional mobility in fibromyalgia patients. Clinical Rheumatology 2012; Aug;31(8):1205-14. 22581278.
3. Toussaint LL, Whipple MO, Abboud LL, et al. A mind-body technique for symptoms related to fibromyalgia and chronic fatigue. Explore: The Journal of Science & Healing 2012; Mar-Apr;8(2):92-8. 22385563.
4. Castel A, Cascon R, Padrol A, et al. Multicomponent cognitive-behavioral group therapy with hypnosis for the treatment of fibromyalgia: long-term outcome. Journal of Pain 2012; Mar;13(3):255-65. 22285609.
5. Ang DC, Kaleth AS, Bigatti S, et al. Research to encourage exercise for fibromyalgia (REEF): use of motivational interviewing, outcomes from a randomized-controlled trial. Clinical Journal of Pain 2013; Apr;29(4):296-304. 23042474.
6. Fontaine KR, Conn L, Clauw DJ. Effects of lifestyle physical activity in adults with fibromyalgia: results at follow-up. JCR: Journal of Clinical Rheumatology 2011; Mar;17(2):64-8. 21325963.
7. Alfano AP, Taylor AG, Foresman PA, et al. Static magnetic fields for treatment of fibromyalgia: a randomized controlled trial. Journal of Alternative & Complementary Medicine 2001; Feb;7(1):53-64. 11246937.
8. van Koulil S, van Lankveld W, Kraaimaat FW, et al. Tailored cognitive-behavioral therapy and exercise training for high-risk patients with fibromyalgia. Arthritis care & research 2010; Oct;62(10):1377-85. 20521308.
9. McCain GA. Role of physical fitness training in the fibrositis/fibromyalgia syndrome. American Journal of Medicine 1986; Sep 29;81(3A):73-7. 3532784.
10. Vitton O, Gendreau M, Gendreau J, et al. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. Human Psychopharmacology 2004; Oct;19 Suppl 1:S27-35. 15378666.
11. Goldenberg DL, Clauw DJ, Palmer RH, et al. Durability of therapeutic response to milnacipran treatment for fibromyalgia. Results of a randomized, double-blind, monotherapy 6-month extension study. Pain Medicine 2010; Feb;11(2):180-94. 20002596.
12. Castro-Sanchez AM, Mataran-Penarrocha GA, Arroyo-Morales M, et al. Effects of myofascial release techniques on pain, physical function, and postural stability in patients with fibromyalgia: a randomized controlled trial. Clinical Rehabilitation 2011; Sep;25(9):800-13. 21673013.
13. Alda M, Luciano JV, Andres E, et al. Effectiveness of cognitive behaviour therapy for the treatment of catastrophisation in patients with fibromyalgia: a randomised controlled trial. Arthritis Research & Therapy 2011; 13(5):R173. 22018333.
14. Pauer L, Winkelmann A, Arsenault P, et al. An international, randomized, double-blind, placebo-controlled, phase III trial of pregabalin monotherapy in treatment of patients with fibromyalgia. Journal of Rheumatology 2011; Dec;38(12):2643-52. 21965636.
15. Arnold LM, Wang F, Ahl J, et al. Improvement in multiple dimensions of fatigue in patients with fibromyalgia treated with duloxetine: secondary analysis of a randomized, placebo-controlled trial. Arthritis Research & Therapy 2011; 13(3):R86. 21668963.
16. Mease PJ, Clauw DJ, Gendreau RM, et al. The efficacy and safety of milnacipran for treatment of fibromyalgia. a randomized, double-blind, placebo-controlled trial.[Erratum appears in J Rheumatol. 2009 Mar;36(3):661]. Journal of Rheumatology 2009; Feb;36(2):398-409. 19132781.
17. Mease PJ, Russell IJ, Arnold LM, et al. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. Journal of Rheumatology 2008; Mar;35(3):502-14. 18278830.
18. Cuatrecasas G, Alegre C, Fernandez-Sola J, et al. Growth hormone treatment for sustained pain reduction and improvement in quality of life in severe fibromyalgia. Pain 2012; Jul;153(7):1382-9. 22465047.
19. Cuatrecasas G, Riudavets C, Guell MA, et al. Growth hormone as concomitant treatment in severe fibromyalgia associated with low IGF-1 serum levels. A pilot study. BMC Musculoskeletal Disorders 2007; 8:119. 18053120.
20. Jones KD, Deodhar AA, Burckhardt CS, et al. A combination of 6 months of treatment with pyridostigmine and triweekly exercise fails to improve insulin-like growth factor-I levels in fibromyalgia, despite improvement in the acute growth hormone response to exercise. Journal of Rheumatology 2007; May;34(5):1103-11. 17407215.

Less Than 3 Months Followup (n=21)

1. Tavoni A, Vitali C, Bombardieri S, et al. Evaluation of S-adenosylmethionine in primary fibromyalgia. A double-blind crossover study. American Journal of Medicine 1987; Nov 20;83(5A):107-10. 3318438.
2. Bagis S, Karabiber M, As I, et al. Is magnesium citrate treatment effective on pain, clinical parameters and functional status in patients with fibromyalgia? Rheumatology International 2013; Jan;33(1):167-72. 22271372.
3. Scudds RA, McCain GA, Rollman GB, et al. Improvements in pain responsiveness in patients with fibrositis after successful treatment with amitriptyline. Journal of Rheumatology - Supplement 1989; Nov;19:98-103. 2481743.
4. Holton KF, Taren DL, Thomson CA, et al. The effect of dietary glutamate on fibromyalgia and irritable bowel symptoms. Clinical & Experimental Rheumatology 2012; Nov-Dec;30(6 Suppl 74):10-7. 22766026.
5. Goldenberg DL, Felson DT, Dinerman H. A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. Arthritis & Rheumatism 1986; Nov;29(11):1371-7. 3535811.
6. Kempenaers C, Simenon G, Vander Elst M, et al. Effect of an antidiencephalon immune serum on pain and sleep in primary fibromyalgia. Neuropsychobiology 1994; 30(2-3):66-72. 7800166.
7. Ozerbil O, Okudan N, Gokbel H, et al. Comparison of the effects of two antidepressants on exercise performance of the female patients with fibromyalgia. Clinical Rheumatology 2006; Jul;25(4):495-7. 16267603.
8. Schwartz TL, Siddiqui UA, Raza S, et al. Armodafinil for fibromyalgia fatigue. Annals of Pharmacotherapy 2010; Jul-Aug;44(7-8):1347-8. 20551299.
9. Ware MA, Fitzcharles MA, Joseph L, et al. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesthesia & Analgesia 2010; Feb 1;110(2):604-10. 20007734.
10. Sanudo B, de Hoyo M, Carrasco L, et al. Effect of whole-body vibration exercise on balance in women with fibromyalgia syndrome: a randomized controlled trial. Journal of Alternative & Complementary Medicine 2012; Feb;18(2):158-64. 22321155.
11. Cook DB, Stegner AJ, Nagelkirk PR, et al. Responses to exercise differ for chronic fatigue syndrome patients with fibromyalgia. Medicine & Science in Sports & Exercise 2012; Jun;44(6):1186-93. 22157881.
12. Passard A, Attal N, Benadhira R, et al. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. Brain 2007; Oct;130(Pt 10):2661-70. 17872930.
13. Roizenblatt S, Fregni F, Gimenez R, et al. Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: a randomized, sham-controlled study. Pain Practice 2007; Dec;7(4):297-306. 17986164.
14. Thomas AW, Graham K, Prato FS, et al. A randomized, double-blind, placebo-controlled clinical trial using a low-frequency magnetic field in the treatment of musculoskeletal chronic pain. Pain Research & Management 2007; 12(4):249-58. 18080043.
15. Casanueva-Fernandez B, Llorca J, Rubio JB, et al. Efficacy of a multidisciplinary treatment program in patients with severe fibromyalgia. Rheumatology International 2012; Aug;32(8):2497-502. 21785956.
16. Miro E, Lupianez J, Martinez MP, et al. Cognitive-behavioral therapy for insomnia improves attentional function in fibromyalgia syndrome: a pilot, randomized controlled trial. Journal of Health Psychology 2011; Jul;16(5):770-82. 21346020.
17. Finset A, Wigers SH, Gotestam KG. Depressed mood impedes pain treatment response in patients with fibromyalgia. Journal of Rheumatology 2004; May;31(5):976-80. 15124260.
18. Affaitati G, Costantini R, Fabrizio A, et al. Effects of treatment of peripheral pain generators in fibromyalgia patients. European Journal of Pain 2011; Jan;15(1):61-9. 20889359.
19. Konuk N, Ortancil O, Bostanci B, et al. A comparison of reboxetine and amitryptilline in the treatment of fibromyalgia syndrome with co-morbid depressive symptoms: An open-label preliminary study. Klinik Psikofarmakoloji Bulteni 2010; 20(1):29-37. 2010535038.
20. Vlaeyen JW, Teeken-Gruben NJ, Goossens ME, et al. Cognitive-educational treatment of fibromyalgia: a randomized clinical trial. I. Clinical effects. Journal of Rheumatology 1996; Jul;23(7):1237-45. 8823699.
21. Hoeger Bement MK, Weyer A, Hartley S, et al. Pain perception after isometric exercise in women with fibromyalgia. Archives of Physical Medicine & Rehabilitation 2011; Jan;92(1):89-95. 21187210.

Other

Post-hoc Subgroup/Exploratory (n=6)

1. Moore RA, Straube S, Paine J, et al. Fibromyalgia: Moderate and substantial pain intensity reduction predicts improvement in other outcomes and substantial quality of life gain. Pain 2010; May;149(2):360-4. 20347225.

2. Pauer L, Atkinson G, Murphy TK, et al. Long-term maintenance of response across multiple fibromyalgia symptom domains in a randomized withdrawal study of pregabalin. Clinical Journal of Pain 2012; Sep;28(7):609-14. 22688598.
3. King SJ, Wessel J, Bhambhani Y, et al. The effects of exercise and education, individually or combined, in women with fibromyalgia. Journal of Rheumatology 2002; Dec;29(12):2620-7. 12465163.
4. Arnold LM, Palmer RH, Ma Y. A 3-Year, open-label, flexible-dosing study of milnacipran for the treatment of fibromyalgia. Clinical Journal of Pain 2013; December;29(12):1021-8. 2013722877.
5. Burckhardt CS, Clark SR, Bennett RM. Long-term follow-up of fibromyalgia patients who completed a structured treatment program versus patients in routine treatment. Journal of Musculoskeletal Pain 2005; 13(1):5-14. 2006152042.
6. Sayar K, Aksu G, Ak I, et al. Venlafaxine treatment of fibromyalgia. Annals of Pharmacotherapy 2003; Nov;37(11):1561-5. 14565792.

Predictors of Treatment Response (n=3)

1. Thieme K, Turk DC, Flor H. Responder criteria for operant and cognitive-behavioral treatment of fibromyalgia syndrome. Arthritis & Rheumatism 2007; Jun 15;57(5):830-6. 17530683.
2. Pae CU, Masand PS, Marks DM, et al. History of early abuse as a predictor of treatment response in patients with fibromyalgia: a post-hoc analysis of a 12-week, randomized, double-blind, placebo-controlled trial of paroxetine controlled release. World Journal of Biological Psychiatry 2009; 10(4 Pt 2):435-41. 19382010.
3. Pae CU, Masand PS, Marks DM, et al. History of depressive and/or anxiety disorders as a predictor of treatment response: a post hoc analysis of a 12-week, randomized, double-blind, placebo-controlled trial of paroxetine controlled release in patients with fibromyalgia. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2009; Aug 31;33(6):996-1002. 19433129.

Duplicate Sample (n=2)

1. Marangell LB, Clauw DJ, Choy E, et al. Comparative pain and mood effects in patients with comorbid fibromyalgia and major depressive disorder: secondary analyses of four pooled randomized controlled trials of duloxetine. Pain 2011; Jan;152(1):31-7. 20598442.
2. Arnold LM, Pritchett YL, D'Souza DN, et al. Duloxetine for the treatment of fibromyalgia in women: pooled results from two randomized, placebo-controlled clinical trials. Journal of Women's Health 2007; Oct;16(8):1145-56. 17937567.

Not Fibromyalgia Per Criteria (n=2)

1. Spitzer AR, Broadman M. A retrospective review of the sleep characteristics in patients with chronic fatigue syndrome and fibromyalgia. Pain Practice 2010; Jul-Aug;10(4):294-300. 20230458.
2. Skouen JS, Grasdal A, Haldorsen EM. Return to work after comparing outpatient multidisciplinary treatment programs versus treatment in general practice for patients with chronic widespread pain. European Journal of Pain 2006; Feb;10(2):145-52. 16310718.

Non U.S. Drug or Treatment (n=2)

1. Drewes AM, Andreasen A, Jennum P, et al. Zopiclone in the treatment of sleep abnormalities in fibromyalgia. Scandinavian Journal of Rheumatology 1991; 20(4):288-93. 1925417.
2. Distler O, Eich W, Dokoupilova E, et al. Evaluation of the efficacy and safety of terguride in patients with fibromyalgia syndrome: results of a twelve-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis & Rheumatism 2010; Jan;62(1):291-300. 20039417.

Review of Another Trial (n=2)

1. Williams DA. Utility of cognitive behavioral therapy as a treatment for insomnia in patients with fibromyalgia. Nature Clinical Practice Rheumatology 2006; Apr;2(4):190-1. 16932684.
2. Mohs R, Mease P, Arnold LM, et al. The effect of duloxetine treatment on cognition in patients with fibromyalgia. Psychosomatic Medicine 2012; Jul-Aug;74(6):628-34. 22753629.

Cannot Differentiate Outcomes (n=1)

1. Fjorback LO, Arendt M, Ornbol E, et al. Mindfulness therapy for somatization disorder and functional somatic syndromes: randomized trial with one-year follow-up. Journal of Psychosomatic Research 2013; Jan;74(1):31-40. 23272986.

Inappropriate Comparison Group (n=2)

1. Rasmussen LB, Mikkelsen K, Haugen M, et al. Treatment of fibromyalgia at the Maharishi Ayurveda Health Centre in Norway II--a 24-month follow-up pilot study. Clinical Rheumatology 2012; May;31(5):821-7. 22278161.
2. Rasmussen LB, Mikkelsen K, Haugen M, et al. Treatment of fibromyalgia at the Maharishi Ayurveda Health Centre in Norway. A six-month follow-up study. Clinical & Experimental Rheumatology 2009; Sep-Oct;27(5 Suppl 56):S46-50. 20074439.

Appendix E. Evidence Tables

Appendix Table E1. Sample selection criteria and allowed co-interventions for included fibromyalgia randomized clinical trials

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Pharmacologic					
Duloxetine					
Arnold, 2012[1] *Efficacy & Safety 30mg duloxetine* US, Mexico, Israel, Argentina Industry-funded	1990 ACR criteria	-Male & Female - ≥18 years -Score ≥4 on average pain severity of BPI-Modified Short Form -Included patients with MDD or GAD, as defined by DSM-IV and confirmed by MINI	-Prior duloxetine treatment -Prior participation in duloxetine study -Substance abuse within past year -Primary psychiatric diagnosis other than MDD/GAD within past year -History of psychosis or bipolar -Clinically judged at risk of suicide -Pregnant or breast-feeding women -Pain symptoms unrelated to FM (could interfere with outcomes) -Regional pain syndromes -Failed back syndrome -Chronic localized pain from past surgery -Rheumatoid, Inflammatory, or infectious arthritis -Autoimmune disease -Patients judged by investigator to be treatment-refractory -Patients with unstable medical conditions or whose response might be compromised by disability compensation	-Medications or herbal agents with primarily CNS activity, regular use of analgesics other than acetaminophen and aspirin, topical lidocaine or capsaicin, antidepressants, anticonvulsants, barbituates, muscle relaxants, chronic use of anti-emetics, hypnotics, and sedatives - <3 months stable therapy of anti-hypertensives, anti-arrhythmics, diuretics, and hormones; steroids other than episodic treatment of symptoms unrelated to FM; benzodiazepine use for FM pain	-Episodic use of some analgesics, such as NSAIDS, was allowed for acute injury or surgery
Arnold, 2010[2] *Flexible Dosed Duloxetine* USA, Puerto Rico Funder not stated: industry is acknowledged; corresponding author is industry-affiliated	1990 ACR criteria	-Male & Female - ≥ 18 years -Score ≥4 on average pain severity of BPI-Modified Short Form at visits 1 and 2 (screening) and visit -Judged to be reliable and had a level of understanding that allowed them to communicate intelligibly and provide informed consent	-Current or diagnosed within last year with any primary psychiatric disorder other than MDD/GAD, as defined by DSM-IV -Clinically judged at risk of suicide -Unstable medical illness likely to require intervention or hospitalization -Pain syndromes unrelated to FM -RheumatoidInflammatory arthritis -Other autoimmune disease -Severe liver disease -Pregnant or breast-feeding	-Analgesics (with the exception of up to 325 mg/day of aspirin for cardiac prophylaxis and acetaminophen up to 2 g/day for pain) -Antidepressants, including tricyclics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs) and SRNI -Encouraged not to initiate or alter ongoing nonconventional/ alternative therapies such as acupuncture, biofeedback, or CBT for study duration	-Patients entering study on stable sleep medications allowed to continue during study -Episodic use (up to 3 nights/week) of chloral hydrate, zolpidem, zopiclone, or zaleplon for sleep

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Russell, 2008[3] *Flexible Dosed Duloxetine* USA, Puerto Rico Industry-funded	1990 ACR criteria	-Male & Female - ≥18 years -Score ≥4 on average pain severity of BPI-Modified Short Form at both screening and baseline -Patients with or without current MDD, were also evaluated for presence of psychiatric disorders using MINI	-Current primary psychiatric diagnosis other than MDD -Pain syndromes unrelated to FM -Regional pain syndromes -Multiple surgeries or failed back syndrome -Rheumatoid/ Inflammatory arthritis -Other autoimmune disease -Unstable medical or psychiatric disorders -Severe liver disease -Pregnant or breast-feeding -Substance abuse within past year -Patients judged by investigator to be treatment-refractory, or whose response might be compromised by disability compensation	-Analgesics (with the exception of up to 325 mg/day of aspirin for cardiac prophylaxis and acetaminophen up to 2 g/day for pain) -Antidepressants, anticonvulsants, or other medications taken for FM or pain -Encouraged not to initiate or alter ongoing nonconventional/ alternative therapies such as acupuncture, biofeedback, or CBT for study duration	-Sedating antihistamines and episodic use (up to 40 total days of use during the 6 months of treatment) of chloral hydrate, zolpidem, zopiclone, and zaleplon were allowed for sleep
Arnold, 2005[4] *Women with or without MDD* USA Industry-funded	1990 ACR criteria	-Females - ≥18 years - Score ≥4 on verage pain severity of BPI-Modified Short Form at both screening and baseline	-Pain from traumatic injury or structural or regional rheumatic disease -Rheumatoid or Inflammatory arthritis -Autoimmune disease -Unstable medical or psychiatric illness -Primary psychiatric diagnosis other than MDD -Primary anxiety disorder within the past year (specific phobias allowed) -Substance abuse within the past year -Serious suicide risk -Pregnancy or breast-feeding -Judged by investigator to be treatment-refractory, or involvement in disability reviews that might compromise response -Severe allergic reactions to multiple medications -Prior participation in duloxetine study	-Medications or herbal agents with primarily CNS activity -Regular use of analgesics with the exception of acetaminophen up to 2 g/day and aspirin for cardiac prophylaxis up to 325 mg/day -Chronic use of sedatives, antiemetics, or antispasmodics -Initiation of or change in unconventional or alternative therapies	Not reported
Arnold, 2004[5] *With or without MDD* USA Industry-funded with industry-	1990 ACR criteria	-Male & Female - ≥18 years -Score 4 on pain intensity item of FIQ at visits 1 and 2 -Judged to be reliable and had an educational level and degree of	-Pain from traumatic injury or structural or regional rheumatic disease -Rheumatoid / Inflammatory arthritis -Autoimmune disease -Unstable medical or psychiatric illness -Dysthymia (more treatment resistant than MDD) -Primary psychiatric diagnosis other than MDD -Substance abuse within the past year -History of psychosis	-Medications or herbal agents with primarily CNS activity -Regular use of analgesics with the exception of acetaminophen up to 2 g/day and aspirin up to 325 mg/day -Chronic use of sedatives, antiemetics, or antispasmodics -Episodic use of anticoagulants	Not reported

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
managed trial implementation and statistical programming support		understanding that allowed them to communicate intelligibly	-Pregnancy or breast-feeding -Unacceptable contraception in those of childbearing potential -Involvement in disability reviews that might compromise response -Use of an investigational drug within 30 days -Prior participation duloxetine study -Severe allergic reactions to multiple medications -Intolerance to >3 psychoactive drugs or >1 SSRI -Failure to respond to ≥2 adequate regimens of 2 different classes of antidepressants for depression or FM	- <3 months stable therapy of antihypertensives, hormones antiarrhythmics, antidiarrheals, antihistamines, cough/cold preparations (excluding dextromethorphan), or laxatives Initiation or change in unconventional or alternative therapies	
Gendreau, 2005[6] USA Industry-supported	1990 ACR criteria	-Ages 18 to 70 -Pain score >10 on a 20-point Gracely scale at baseline -Willing to use a contraceptive, if female, and to withdraw from all central nervous system-active therapies	- Psychosis -Active suicidality -Alcohol or substance abuse -Concurrent auto-immune, inflammatory, infectious or malignant disorder -Known sleep apnea or prostatic hypertrophy -Abnormal baseline liver or kidney function tests	-Antidepressants -Antiepileptics -Centrally-acting Muscle Relaxants -Hypnotics -Opiods and their derivatives -Fluoxetine	-Stable dose of NSAIDS, Aspirin, and Acetaminophen
Off-label					
Arnold, 2002[7] *Flexible-dose Fuloxetine* USA Industry-funded	1990 ACR criteria	-Females only - ≥18 years	- Evidence of traumatic injury - Inflammatory rheumatic disease - Infections or endocrine-related arthopathy - Clinically unstable medical illness - History of seizure, head trauma, or stroke - Lifetime history of hypomania, mania, psychosis, or dementia - Alcohol/substance dependence in past 6 months - Substantial risk of suicide - Current Axis I diagnosis (per the DSM-IV) - Score of ≥10 Hamilton Depression Rating Scale	- Monoamine oxidase inhibitors, tricyclics, lithium, SSRIs, or other antidepressants within 2 weeks before randomization - Investigational medications within 3 months before randomization Previously received fluoxetine for FM	- Acetaminophen or nonsteroidal anti-inflammatory medications on their usual schedule
Stening, 2011[8] Sweden	1990 ACR criteria	-Ages 49 to 60 -BMI <30 -Post-menopausal state for at least 6	-History of thromboembolism -Diabetes Mellitus -Polyneuropathy -Chronic liver disease	-Anti-psychotics -Pro re nata ("unforeseen need") medications 24 hours before sensory testing	-Daily prescribed analgesics (except opiates) -Anti-depressants

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Industry funded		months and had normal mammography screening during preceding year	-Alcohol or substance abuse -Hemoglobinopathy -Endometrial adenomatous hyperplasia or malignancy -Presence of untreated hypertension (>160/95) -Undiagnosed vaginal bleeding	-Opiates	
Sadreddini, 2008[9] Iran No funding information	1990 ACR criteria	Postmenopausal women within 6 months before the onset of the study	-Other significant problem that causes secondary FM -Severe osteoporosis based on radiographies or DEXA (Dual X-ray Absorptiometry) examination -Prior history of thrombotic events -Prior history of breast or genital neoplasm -Immobile patients	Antidepressants	No information
Physical					
Assis, 2006[10] Brazil Government-funded	1990 ACR criteria	-Age 18-60 -Literate -Kept in an unchanged drug regimen for at least 4 weeks prior to study	-Symptomatic cardiac failure -Uncontrolled thyroid disturbances -BMI ≥40 -Infectious contagious skin disease -Coronary disease -Pulmonary disease -Neurologic disease -Rheumatic disease limiting ability to exercise -Those who performed regular physical activity in the 6 weeks before trial	No information	Acetaminophen as rescue medication
Gusi, 2010[11] Spain No funding information	1990 ACR criteria	Patients meeting 1990 ACR criteria	-History of severe trauma -Frequent migraines -Peripheral nerve entrapment -Inflammatory rheumatic disease -Severe psychiatric illness -Other diseases that prevent physical loading -Pregnancy -Participation in other physical or psychological therapy program more than once a week for ≥30 minutes during a 2week period in last 5 years -Participation in other therapies (manual and/or psychological treatment) that could influence the current intervention	No information	No information
Hakkinen, 2002[12] Finland	1990 ACR criteria	No additional information except that subjects were	No information	No information	No information

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
No funding information		habitually physically active, but had no background in strength training			
Senna, 2012[13] (non exercise) Egypt No funding information	1990 ACR criteria	No information	-Medical disorder that would affect body weight -Inflammatory arthritis -Autoimmune disease -Unstable medical or psychiatric illness -Regimen that has not been stable for at least 2 months prior to baseline -Pregnant women or attempting to conceive -Antidepressant medication or sleeping pills	-Antidepressants -Sleeping pills	Medications prescribed by physician
Valkeinen, 2008[14] Finland Government and foundation support	Not reported	Women >50 years	-Severe cardiovascular disease -Diabetes -Severe osteoarthritis of the large joints -Thyroid gland disorders -Any disease that might confound results -Participation in regular and aerobic and strength training and predictable difficulties for attending training sessions	No information	Previous medications for FM and other diseases such as analgesics, antidepressants and hormonal-replacement therapy
Psychological					
Junghaenel, 2008[15] USA Foundation funded	Not reported	-Female -FM diagnosis	No information	No information	Not reported
Scheidt, 2013[16] Germany Industry Funded	-1990 ACR Criteria -ICD-10	-Female -18-70 years -Patients meeting 1990 ACR criteria for FM -diagnosis of comorbid depression or anxiety disorder	-Severe or life threatening diseases -Psychiatric or neuropsychiatric conditions associated with cognitive impairment and/or suicidal ideation -Current psychotherapy or participation in other clinical trials	No information	-Antidepressants if patient has co-morbid depression -Analgesics
Castel, 2012[17] Spain No funding	1990 ACR criteria	-Age 18-65 -Patients meeting 1990 ACR criteria for FM	-1 or more additional severe chronic medical pain conditions -Significant suicidal ideation -Severe psycho-pathology -Moderate-to-severe cognitive impairment	No information	-Analgesics -Anti-depressants -Anti-convulsants -Myorelaxants

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
information					
Edinger, 2005[18] USA Government funded (NIAMS)	1990 ACR criteria	-Age 21-65 -Patients meeting 1990 ACR criteria for FM -Structured interview criteria for insomnia -Have 60 minutes or more of total nocturnal wake time on average over 1 week of sleep log monitoring	-Currently pregnant, breastfeeding, or not practicing contraception -Comorbid sleep-disruptive medical condition -Meeting structured interview criteria for an Axis I depressive (other than dysthymia), anxiety, or substance abuse disorder -Severe hypnotic dependence, suggested by the use of a hypnotic agent in a higher than recommended dosage or repeated episodes of rebound insomnia on withdrawal - symptoms of sleep apnea, restless legs syndrome, or circadian rhythm disorder - apnea-hypopnea index or periodic limb movement (PLM)-related arousal index of 15 or more per hour on a screening polysomnogram	No information	-Anti-depressants -Analgesics
Mixed					
Fontaine, 2010[19] USA Government funded (NIAMS)	1990 ACR criteria	-Age 18 or older -Patients meeting 1990 ACR criteria for FM.	-Acute or chronic medical conditions -Intention to change medication that might affect mood -Intent to seek professional treatment for anxiety or depression	No information	No information
Lera, 2009[20] Spain No funding info	1990 ACR criteria	-Female -Patients meeting 1990 ACR criteria for FM	-Litigation against government for disability pensions -Suffering from severe depression, psychosis, or delusional disorder	No information	Analgesics

Abbreviations: **ACR**-American College of Rheumatology **BDI**-Beck Depression Inventory **BMI**-Body Mass Index **BPI**-Brief Pain Inventory **CBT**-Cognitive Behavioral Therapy **CNS**-Central Nervous System **DEXA**-Dual X-ray Absorptiometry **DVD**-Digital Video Disk **DSM-IV** -Diagnostic and Statistical Manual of Mental Disorder-Fourth Edition **FIQ**-Fibromyalgia Impact Questionnaire **FM** – Fibromyalgia **GAD**-Generalized Anxiety Disorder **ICD-10** – International Classification of Diseases – version 10 **MDD**-Major Depressive Disease **MINI**-Mini International Neuropsychiatric Interview **NIAMS**: National Institute of Arthritis and Musculoskeletal and Skin Diseases **NSAID**-Non-steroidal Anti-inflammatory Drug **PLM**-Periodic Limb Movements **SSRI**-Selective Serotonin Reuptake Inhibitors **SNRI**-Serotonin-norepinephrine reuptake inhibitor

Appendix Table E2. Sample selection criteria and allowed co-interventions for included pooled studies of patient-level randomized clinical trial data

Author, Year, Country, Funder, Studies Pooled	Diagnostic Criteria	Additional Inclusion Criteria*	Exclusion Criteria*	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Pharmacologic					
Duloxetine					
Bennett, 2012[21] USA, Puerto Rico, Germany, Spain, Sweden, United Kingdom Industry funded **Pooled**: Chappell, 2008[22] Russell, 2008[3] Arnold, 2005[4] Arnold, 2004[5]	1990 ACR criteria	-Male & Female (Female only in Arnold, 2005[4]) - ≥18 years -With or without MDD as defined by DSM-IV -Score ≥4 on either pain intensity item of FIQ (Arnold, 2004[5]) or average pain severity of BPI-Modified Short Form (Arnold, 2005,[4] Russell, 2008,[3] and Chappell, 2008[22])	-Current or prior duloxetine treatment -Current primary psychiatric (Axis I) diagnosis other than MDD as defined by DSM-IV, including current or past diagnosis of dysthymia -History of psychosis, bipolar disorder, or schizoaffective disorder -Any anxiety disorder as primary diagnosis within past year -Pain symptoms related to traumatic injury, structural rheumatic disease, or regional rheumatic disease (e.g., osteoarthritis, tendinitis) -Regional pain syndrome -Multiple surgeries or failed back syndrome -Current or previous rheumatoid arthritis, inflammatory arthritis, or autoimmune disease -Any serious medical illness	Not reported (in pooled manuscript)	Not reported (in pooled manuscript)
Bradley, 2010[23] USA, Puerto Rico, Germany, Spain, Sweden, United Kingdom Industry funded **Pooled**: Chappell, 2008[22] Russell, 2008[3] Arnold ,2005[4] Arnold, 2004[5]	1990 ACR criteria	-Male & Female (Female only in Arnold, 2005[4]) - ≥18 years -Score ≥4 on either pain intensity item of FIQ (Arnold, 2004[5]) or average pain severity of BPI-Modified Short Form (Arnold, 2005,[4] Russell, 2008,[3] and Chappell, 2008[22])	-Serious or unstable medical or psychiatric illness -Current primary psychiatric diagnosis other than MDD -Primary diagnosis of anxiety within past year -Pain from traumatic injury -Rheumatologic illness	Not reported (in pooled manuscript)	Not reported (in pooled manuscript)
Arnold, 2009[24] USA, Puerto Rico, Germany, Spain, Sweden, United Kingdom	1990 ACR criteria	-Male & Female - ≥18 years -With or without MDD, diagnosed by MINI -Score ≥4 on average pain severity of BPI-	-Pain from traumatic injury or structural or regional rheumatic disease -Rheumatoid arthritis, inflammatory arthritis, or autoimmune disease -Unstable medical of psychiatric illness -Current primary psychiatric diagnosis other than	-Medications or herbal agents with CNS activity (including anti-depressants) -Regular use of analgesics other than	Not reported (in pooled manuscript)

Author, Year, Country, Funder, Studies Pooled	Diagnostic Criteria	Additional Inclusion Criteria*	Exclusion Criteria*	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Industry funded **Pooled**: Chappell, 2008[22] Russell, 2008[3] Arnold, 2005[4] Arnold, 2004[5]		Modified Short Form	MDD -Primary anxiety disorder within the past year -Serious suicide risk -Pregnancy or breastfeeding -Patients, who, in the opinion of the investigator, were treatment refractory or may have had involvement in disability reviews that may compromise treatment response -Severe allergic reaction to multiple medications -Prior participation in duloxetine study	acetaminophen and aspirin -Chronic use of sedatives, antiemetics, or antispasmodics -Initiation or change in unconventional or alternative therapies	
Milnacipran					
Arnold, 2012[25] USA, Canada Industry Funded **Pooled**: Arnold, 2010[26] Mease, 2009[27] Clauw, 2008[28]	1990 ACR criteria	-Male & Female -18-70 years -Mean VAS Score ≥40 or 50 at end of baseline period (0-100 scale) -Score ≥4 on FIQ physical function component (Arnold, 2010,[26] Clauw, 2008[28]	Not reported in article. Source articles indicate: Clauw, 2008[28] -Experimental agent in past 30 days or had prior exposure to milnacipran -Severe psychiatric illness or current MDD episode (MINI or BDI score >25) -Significant suicide risk -History of drug abuse -History of behavior that would prohibit compliance for duration of study -Active cardiovascular, pulmonary, hepatic, renal, GI, or autoimmune disease (except Hashimoto's or Graves' disease that had been stable for 3 months before screening) -Current systematic infection -Active cancer (except basal cell carcinoma) -Unstable endocrine disease -Severe sleep apnea -Prostate enlargement/other GU disorder (males) -Pregnancy or breastfeeding -Unacceptable contraception Mease, 2009[27] -Severe psychiatric illness or current MDD -Significant suicide risk -History of alcohol or drug abuse -Active cardiovascular, respiratory, endocrine, genitourinary, liver, or kidney disease -Active peptic ulcer or inflammatory bowel disease -Autoimmune disease	-Centrally acting medications used to manage fibromyalgia symptoms, such as anti-depressants, anticonvulsants, opioids, and muscle relaxants	-Weight-related interventions not specifically prohibited

Author, Year, Country, Funder, Studies Pooled	Diagnostic Criteria	Additional Inclusion Criteria*	Exclusion Criteria*	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
			-Cancer or current chemotherapy -Significant sleep apnea -Pregnancy or breastfeeding -Unacceptable contraception Arnold, 2010[26] -Rheumatic or medical disorders with symptoms similar to FM -Prior milnacipran or investigational drug in past 30 days -Current MDD as defined by MINI -BDI score >25 at screening or randomization -Significant suicide risk -Lifetime history of psychosis, hypomania or mania, substance abuse, other severe psychiatric illness -History of behavior that would prohibit compliance for duration of study -Active or pending disability claim, worker's compensation claim, or litigation -Active or unstable medical illness -Prostate enlargement or other GU disorder (men) -Pregnancy or breastfeeding -Unacceptable contraception		
Geisser, 2011[29] USA Industry Funded **Pooled**: Mease, 2009[27] Clauw, 2008[28]	1990 ACR criteria	-Male & Female -18–70 years -Score ≥50 (Mease, 2009[27] or ≥40 (Clauw, 2008[28]) on mean 24-hour recall VAS pain intensity recording on a scale of 0-100 (measured on an electronic PED)	-Severe psychiatric illness or a current major depressive episode, as defined by MINI -Active cardiac, hepatic, renal, or immune disorder -Active cardiovascular, respiratory, endocrine, genitourinary, liver, or kidney disease -Autoimmune disease	-Central nervous system-active pharmacologic therapies commonly used for FM (anti-depressants, anticonvulsants, dopamine agonists, mood stabilizers, muscle relaxants, opioids) -Nonpharmacologic treatments such as transcutaneous electrical nerve stimulation, biofeedback, tender and trigger point injections, acupuncture	Not reported (in pooled manuscript)
Pregabalin					
Arnold, 2010[30]	1990 ACR	-Male & Female	-Any active inflammatory disorder or painful	-Medications taken for	-Acetaminophen only

Author, Year, Country, Funder, Studies Pooled	Diagnostic Criteria	Additional Inclusion Criteria*	Exclusion Criteria*	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
USA Industry-funded **Pooled**: Arnold, 2008[31] Mease, 200[32] Crofford, 2005[33]	criteria	- ≥18 years -At both screening and randomization: score ≥40 mm on a 100-mm pain VAS, and average pain score of ≥4 on a daily pain diary 11-point rating scale based on at least 4 entries in week before randomization	conditions that may confound assessment of FM pain -Unstable medical disorder -Creatinine clearance ≤60 ml/minute - Clinically significant or unstable psychiatric conditions (medical history of or investigator judgment)	pain and sleep disorders -Other psychotropics	rescue analgesic permitted
Bhadra, 2010[34] USA, Canada, Mexico, Denmark, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, United Kingdom, India, Korea, Australia, Venezuela Industry-funded **Pooled**: Arnold, 2008[31] Mease, 2008[32] Crofford, 2005[33] Pauer, 2008[35]	1990 ACR criteria	-Male & Female - ≥18 years -FM duration at least 3 months -In week prior to randomization, score of ≥4 on a daily pain diary 11-point rating scale - At both screening and randomization, score ≥40 mm on a 100-mm pain VAS of the short-form McGill Pain Questionnaire -At least 1 post-baseline score	-Creatinine clearance ≤60 ml/minte -Active inflammatory or rheumatological disorders or painful conditions that may confound assessment of FM pain -Unstable medical or psychological disorder	Not reported (in pooled manuscript)	Not reported (in pooled manuscript)

Author, Year, Country, Funder, Studies Pooled	Diagnostic Criteria	Additional Inclusion Criteria*	Exclusion Criteria*	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Byon, 2010[36] USA, Canada, Mexico, Denmark, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, United Kingdom, India, Korea, Australia, Venezuela Industry-funded **Pooled**: Arnold, 2008[31] Mease, 2008[32] Crofford, 2005[33] Pauer, 2008[35]	1990 ACR criteria	-Male & Female - ≥18 years -FM duration at least 3 months -Creatinine clearance (CLcr) >60 mL/minute -At both screening and randomization, score ≥40 mm on a 100-mm pain VAS of the short-form McGill Pain Questionnaire -In week prior to randomization, score of ≥4 on a daily pain diary 11-point rating scale; and completion of at least 4 pain diary days during baseline phase	-Those reporting >30% decrease on pain VAS during 1-week placebo run-in excluded from randomization (placebo responders) (Arnold, 2008[31] and Pauer, 2008[35])	Not reported (in pooled manuscript)	Not reported (in pooled manuscript)

Abbreviations: **BDI**-Beck Depression Inventory; **BPI**-Brief Pain Inventory; **CNS**-Central nervous system; **DSM-IV**-Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, **FIQ**-Fibromyalgia Impact Questionnaire, **GI**-gastrointestinal; **GU**-Genitourinary; **MDD**-Major Depressive Disorder; **MINI**-Mini International Neuropsychiatric Interview, **PED**-Patient experience diary**; VAS**-Visual Analog Scale 24-hour recall pain score

***Usually determined from source documents since selection criteria were often missing in pooled articles

Appendix Table E3. Sample selection criteria and allowed co-interventions for included fibromyalgia observational studies

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Pharmacologic					
Arnold, 2012[37] USA, Canada Industry funded	1990 ACR criteria	-Male & Female -18-70y -Score ≥ 4 on FIQ physical function raw score (range: 0-33) at screening and between 40-90 on VAS pain scale (range: 0-100) during 14-d baseline period	-Other rheumatic or medical disorders with symptoms similar to FM -Previous exposure to milnacipran -Treatment with an investigational drug within 30 days of screening -BDI >25 (moderate-to-severe depressive symptoms) or current MDD as assessed by MINI -Significant risk of suicide -History of psychosis, hypomania, or mania -Substance abuse -Other severe psychiatric disorder as assessed by investigator -History of behavior that would prohibit compliance for duration of study as assessed by investigator -Pregnancy or breastfeeding -Unacceptable contraception -Any active or unstable medical condition -Prostate enlargement or other genitourinary disorder -Active or pending disability claim, worker's compensation claim, or litigation	-Digitalis -Centrally acting medications for FM -Transcutaneous electrical nerve stimulation, biofeedback, tender and trigger point injections, acupuncture, and anesthetic or narcotic patches	-Acetaminophen, aspirin, and nonsteroidal anti-inflammatory agents -Short term pain rescue medication included tramadol or hydro-codone between randomization and week 4 -Triptans permitted for acute migrant treatment -Nonbenzodiazepine hypnotic agents for treatment of insomnia
Younger, 2009[38] USA Nonprofit/ foundation funded	1990 ACR criteria	-Held drug dosages steady for at least 2 previous months	-Joint pain/inflammation -History of autoimmune or rheumatologic condition -Blood test results: RF >20IU/mL, antinuclear antibody >1:80, and ESR >60 mm/hour	-Current or recent use of opioids	-Medications other than opioids -Asked not to modify pain treatment regimen without notifying study personnel
Physical					
Drexler, 2002[39] Austria Funding not reported	1990 ACR criteria	Not reported	Not reported	Not reported	Not reported

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Mixed					
Joshi, 2009[40] India No external funding support	1990 ACR criteria	-Male & Female -18-60 years -Symptoms of chronic muscular pain for at least 12 weeks	-Pregnant or lactating -History of trauma, fractures, fever, malignancy, chronic renal or hepatic disorders -Alcohol abuse -Cerebrovascular or neurological abnormality	Not reported	-Allowed to continue previous medications and exercise regimens, if any

Abbreviations: **ACR**-American College of Rheumatology; **BDI**-Beck Depression Inventory; **ESR**-erythrocyte sedimentation rate; **FIQ**-Fibromyalgia Impact Questionnaire; **FM**-Fibromyalgia; **MDD**-Major Depressive Disorder, **MINI**-Mini International Neuropsychiatric Interview, **RF**-rheumatoid factor, **VAS**-Visual Analog Scale 24-hour recall pain score

Appendix Table E4. Fibromyalgia randomized clinical trials with subgroups and mixed samples, by class of treatment

Author, Year, Country, Funder*	Study Aim	Subgroup, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control Group	Subgroup Outcomes	Followup Duration	Reported Results
Pharmacologic							
Duloxetine							
Arnold, 2012[1] *Efficacy & Safety* USA, Mexico, Israel, Argentina Industry-funded	Assess efficacy and safety of duloxetine in reducing pain severity	**Age:** <65, ≥65 (n NR) **Sex** F: 293 (95) **Race** W: 269 (87) NW: 39 (13) NW: Tx: 22 (14) NW C: 17 (11) **MDD**: 69 (22) Tx: 37 (54) C: 32 (46) **GAD**: 19 (6) Tx: 8 (42) C: 11 (58)	N: 308 Tx: 155 C: 153 M: 5% 51 years	**Tx**: Duloxetine 30 mg/day x 12 weeks **C**: Placebo	Primary: BPI Secondary: PGI-I, FIQ	3 months	Subgroups: Text summary only; data not shown. Treatment by subgroup interactions not significant except race (NW>W) for BPI pain improvement. Subgroup attrition not reported. AEs not reported by subgroup. Overall: No significant difference in BPI pain in treated vs. controls. Global symptoms and function improved on drug. Study powered for main treatment effect only. Overall attrition 25% (22% treated, 28% control).No difference in serious AEs between groups. More treatment-emergent AEs in treated (65% vs. 52% control). Most common AEs: nausea, dry mouth, somnolence, insomnia.
Arnold, 2010[2] *Flexible Dose* USA, Puerto Rico Industry-funded	Investigate efficacy of duloxetine on changes in FM symptoms	**Age**: (n NR) **Sex** F: 494 (93), **Race** W: 410 (77) **MDD**: 97 (18) Tx: 44 (17) C: 53 (20) **GAD**: 43 (8) Tx: 19 (7) C: 24 (9)	N: 530 M: 7% 50 years	Titration to **Tx**: Duloxetine 60 or 90 or 120 mg/day x 12 weeks **C**: Placebo	PGI-I	3 months	Subgroups: Text summary only with p values; data not shown. All treatment by subgroup interactions on PGI-I were not significant. Subgroup attrition not reported. AEs not reported by subgroup. Overall: Duloxetine reduced (improved) PGI-I in treated vs. controls. Study powered for main treatment effect only. Overall attrition 32% (33% treated, 30% controls). No difference in serious AEs between groups. Higher proportion treated had AEs vs.

Author, Year, Country, Funder*	Study Aim	Subgroup, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control Group	Subgroup Outcomes	Followup Duration	Reported Results
							controls (83% vs 73%). Most common AEs: nausea, headache, constipation, dry mouth, dizziness, diarrhea
Russell, 2008[3] USA, Puerto Rico Industry-funded	Assess efficacy and safety of duloxetine for pain in FM patients with/without major depressive disorder	**Age:** <65, ≥65 (n NR) **Sex** F: 493 (95) **Race** W: 438 (84) **MDD:** 126 (24) **T_1**: 22 (28) **T_2**: 35 (23) **T_3**: 34 (23) **C**: 35 (24)	N: 520 M: 5.2% 52 years	**T_1**: Duloxetine 20 mg/day **T_2**: Duloxetine 60mg/d **T_3**: Duloxetine 120 mg/day x 15 weeks **C**: Placebo	Primary: BPI, PGI-I Secondary: FIQ, CGI-S, TPs, MFI, HAMD, SDS, SF-36, EQ5D	6 months	Subgroups: Treated patients with and without MDD had similar improvements in BPI pain and PGI-I vs. controls at 3 and 6 months. Treatment by subgroup interactions not significant for age, sex, and race at 3 or 6 months (p-values only; no data). P-values for treatment-MDD interactions not reported. Mean change from baseline in BPI and PGI-I by treatment group for with/without MDD are shown (3 and 6 mo.). Study powered for main treatment effect only. Subgroup attrition not reported. AEs not reported by subgroups. Overall: Higher doses had more dropouts. Few men per group (2-14). Attrition reported segmentally (0-3 mo. and 4-6 mo.), not overall. Attrition 37% through month 3 (38%=T_1, 35%=T_2, 35%=T_3; 42% in controls). Attrition 15% months 4-6 using denominator after third month (10%=T_1, 15%=T_2, 17%=T_3;14% in controls). No difference in SAEs between groups. Proportion who discontinued due to AEs in 6 months differed by group (11% T_1, 15% T_2, 27% T_3, 13% control). Most common AEs: nausea, dry mouth, constipation, somnolence, fatigue.

Author, Year, Country, Funder*	Study Aim	Subgroup, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control Group	Subgroup Outcomes	Followup Duration	Reported Results
Arnold, 2005[4] *Women with or without MDD* USA Industry-funded	Efficacy and safety of duloxetine in women with or without current MDD Test daily vs. 2x/day dosing	**MDD**: 92 (26%) **T_1**: NR **T_2**: NR **C**: NR "NSD across groups in MDD at baseline." Criteria to determine MDD at baseline not specified	N: 354 M: 0% 49 years	**T_1**: Duloxetine 60mg/day **T_2**: Duloxetine 120 mg/day x 12 weeks **C**: Placebo	Primary: BPI Secondary: FIQ, TPs, CGI-S, PGI-I, clinician-rated $HAMD_{17}$, Depression QoL, SF-36, SDS	3 months	Subgroup: Text summary only; data not shown. Treatment by MDD interaction not significant; effect of duloxetine on pain (BPI) was similar in patients with and without MDD. Study powered for main treatment effect only. Subgroup attrition not reported. AEs not reported by subgroups. Overall: Higher dose had more dropouts from AEs. Overall attrition 39% (35%=T_1, 39%=T_2; 43% controls). No difference in SAEs between groups. Significantly more treated reported TEAEs (92% T_1, 91% T_2, 79% control). Most common AEs nausea, dry mouth, constipation, diarrhea.
Arnold, 2004[5] *with or without MDD* USA Industry-funded & managed	Efficacy and safety of duloxetine in patients with or without current MDD	**Sex** F: 184 (89) **MDD**: Yes:79 (38) Tx: 42 (41) C: 37 (36)	N: 207 M: 11.1% 49 years	**Tx**: Duloxetine 120 mg/day x 12 weeks **C**: Placebo	Primary: FIQ (total and pain scores), Secondary: FIQ fatigue), BPI, CGI-S, PGI-I, SF-36, BDI,SDS, TPs	3 months	Subgroups: Text summary only; subgroup data not shown. Women had nonsignificant improvement in FIQ pain and total FIQ. Treatment-sex interaction significant in women for BPI and Sheehan Disability improvement; no difference in any outcome between treated and untreated males. Drug improved FM symptoms and pain regardless of MDD. Study powered for FIQ pain main effect, not treatment-subgroup interactions. Subgroup attrition not reported. AEs not reported by subgroups. Overall: Duloxetine significantly reduced (improved) FIQ total pain score in treated vs controls; other outcomes not

Author, Year, Country, Funder*	Study Aim	Subgroup, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control Group	Subgroup Outcomes	Followup Duration	Reported Results
							significant. Overall attrition 40% (44% treated, 36% controls). No difference in SAEs between groups. Significantly more treated reported TEAEs (90% vs. 75%). Most common TEAEs insomnia, dry mouth, and constipation.
Milnacipran							
Gendreau, 2005[6] USA Industry-funded	Evaluate safety and efficacy of milnacipran in FM treatment	**Depression:** 20 (16%) **T_1**: 8 (16) **T_2**: 3 (7) C: 9 (32) Assessed by MINI	N: 125 M: 2-4% 47 years	Titrated up to: **T_1**: Milnacipran 100 mg, 2x/day **T_2**: Milnacipran 200 mg, 1x/day **C**: Placebo	E-diary pain score, Gracely pain, VAS pain, McGill	3 months	Subgroups: Incomplete outcomes reporting for subgroup. Outcomes reported by 50% pain responders, not by depression alone. More placebo patients had depression than in either treatment group. No differences in pain in 2x/day-treated depressed vs. nondepressed patients. More depressed patients had a positive response to placebo than nondepressed. Article Table 3 lacks 1x/day-dosed group outcomes. Most frequent reason for dropout was AEs (14.4%). No information on power was reported. Subgroup attrition not reported. AEs not reported by subgroup. Overall: Improvements in pain were greater in treated vs control in 9 of 13 outcomes. Overall attrition 28% (27%=T_1, 30%=T_2; 25% in controls). Significantly more treated discontinued study prior to endpoint due to AEs (14%=T_1, 22%=T_2; 4% controls). Most common AEs: headache, GI complaints (nausea, abdominal pain, constipation).

Author, Year, Country, Funder*	Study Aim	Subgroup, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control Group	Subgroup Outcomes	Followup Duration	Reported Results
Off-label							
Arnold, 2002[7] *Fluoxetine* USA Industry-funded	Efficacy of fluoxetine in the treatment of FM	**Depression:** 37/60 (62%): Tx: 17/30 (57%) C: 20/30 (67%)	N: 60 M: 0 46 years	**Tx**- Fluoxetine 10-80 mg/d x 12 weeks **C**: Placebo	FIQ (total and pain scores); Secondary: McGill Pain, change in TPs, total myalgia score	3 months	Subgroup: Text summary only; data not shown. Treatment by subgroup interaction with history of MDD or baseline level of depression not statistically significant on FIQ. AEs not reported by subgroups. Study powered for main effect only. Overall: Fluoxetine reduced (improved) FIQ scores (total, pain) in treated vs. controls. Overall attrition 38% (37% treated, 40% controls). No difference in AEs in treated vs. controls. Most common AEs: headache, insomnia, sedation, nausea.
Psychological							
Junghaenel, 2008[15] USA Foundation-funded, with material support through academic institution	Identify differential health benefits of written emotional disclosure	**Coping style** from baseline MPI: 1. Adaptive coping (AC): 41 (45) T: NR C: NR 2. Dysfunctional (DYS): 15 (16) T: NR C: NR 3. Interpersonally distressed (ID): 36 (39) T: NR, C: NR **Educational level <high school** T: 7 (23) C: 21 (34) **Any college** T: 19 (61)	N: 92 T: 31 C: 61 M: 0% 50 years	**T**: Written emotional disclosure (WED): three 20 minute writing sessions in lab focusing on emotional expression and cognitive reappraisal of stressful event. **C**: Neutral writing about daily activities or usual care.	Pain, fatigue, psychological well-being	4 months	Subgroup: Treatment by subgroup interactions not significant for pain or fatigue outcomes. Interaction for psychological wellbeing "trended" toward significance (p=0.08); interpersonally distressed (ID) patients improved more than adaptive coping per baseline group. Only graduate educated had significant improvement in psychological wellbeing (p<0.0001) compared to college (p=0.53) or less (p=0.33) education. Study not powered for subgroup treatment effect. Attrition not specified in text or tables for subgroups or overall. AEs not reported for subgroups or overall.

Author, Year, Country, Funder*	Study Aim	Subgroup, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control Group	Subgroup Outcomes	Followup Duration	Reported Results
		C: 30 (49) **Graduate** T: 5 (16) C: 10 (16)					
Mixed							
Lera, 2009[20] Spain No funding information	Analyze response of FM patients to two multidisciplinary treatments	Comorbid fatigue: 16 (24) T: 9 (56) C: 7 (44)	N: 66 T: 35 C: 31 M: 0% 51.1 years	**Tx**: Multidisciplinary treatments (medical, physical training, education and discussion) and CBT 90 minute sessions/week x 15sessions **C**: Multidisciplinary treatments (including pharmacological treatment + 1hour/week 14 group sessions x 4 months)	FIQ, SF-36, SCL-90-R	15 weeks	Subgroup: Fatigued patients showed a better response with (MT plus CBT) than with MT alone. Study not powered to show subgroup treatment effect. Subgroup attrition not reported. AEs not reported for subgroup. Overall: Significant fall in FIQ score. Greater improvement in daily functioning and health status in treatment group. Underpowered study. Overall attrition 20% (19% in treated, 23% in controls). AEs not reported.

* See Appendix Tables E13-E16 for further funding details.

Abbreviations: **AE**-Adverse Effects; SAE-Serious Adverse Event; TEAE-Treatment Emergent Adverse Event; **BPI**-Brief Pain Inventory; **C**-Control; **CBT**-Cognitive Behavioral Therapy; **CGI-S** - Clinical Global Impression of Severity Scale; **DYS** – Dysfunctional; **E**-diary-Electronic diary; **EQ-5D**- EuroQol health outcomes assessment; **F**-Female; **FIQ**-Fibromyalgia Impact Questionnaire; **FM**-Fibromyalgia; **GAD**-Generalized Anxiety Disorder; **HAMD**- Hamilton Rating Scale for Depression; **ID**- Interpersonally Distressed; **M**-Male; **MDD**-Major Depressive Disease; **MFI**- Multidimensional Fatigue Inventory; **MT**-Multidisciplinary Treatment; **MINI**- Mini International Neuropsychiatric Interview mg: milligrams; **MOS**-Medical Outcomes Study sleep scale; **NR**-Not Reported; **NSD**-No Significant Difference; **NW**-Non-White; **PGI-I -** Patient Global Impression of Improvement Scale; **QoL**-Quality of Life; **SCL-90-R** - Symptom Checklist-90-Revised; **SDS**- Sheehan Disability Scale; **SF-36**- MOS Short-Form 36-item Health Survey; $\mathbf{T_x}$-Treatment group $\mathbf{T_1}$-Treatment group 1 $\mathbf{T_2}$-Treatment group 2 $\mathbf{T_3}$-Treatment group 3 **TPs**-Tender Points **VAS**- Visual Analogue Scale **WED**-Written Emotional Disclosure; **W**-White

SAEs- serious adverse events per authors, **TEAEs**- treatment-emergent adverse events per authors

Appendix Table E5. Fibromyalgia randomized clinical trials with pure subgroup samples, by class of treatment

Author, Year, Country, Funder	Study Aim	Subgroup, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Subgroup Outcomes	Followup Duration	Reported Results
Pharmacologic							
Off-label							
Stening, 2011[8] Sweden Funded by Government, Foundation & Academic	Effect of transdermal estrogen on pain	Postmenopausal women (all)	N: 29 M: 0 54 years	Tx:Transdermal 17B-estradiol 50 ug/day x 8 weeks C:placebo	Modified Pain Map, Quantitative sensory testing	5 months	No difference between groups on self-estimated pain. Only half of the planned sample size was enrolled. More patients on antidepressants in placebo group (45% vs. 13% treated). Overall attrition 14%; (0% treated, 28% controls).
Sadreddini, 2008[9] Iran No funding information	Compare Raloxifen (Evista) with placebo in treatment of FM	Postmenopausal women (all)	N: 100, M: 0%, 53.2 years	Tx: Raloxifen 60 mg/day x 16 weeks C: Placebo	Stanford HAQ, IHAD (Iranian), Sleep Disturbance, VAS, TPs	16 weeks	Treated patients had greater pain reduction in all measures except anxiety and depression (IHAD). Placebo group was significantly older than treated. Overall attrition 4% (2% treated, 6% controls). No difference in AEs in treated vs. controls. Most common AEs were increased anxiety, leg cramps, flushing, & drowsiness
Physical							
Assis, 2006[10] Brazil Government-funded	Compare clinical effectiveness of water-based vs. land-based aerobic exercise for FM	Sedentary women (had not performed "regular physical activity" for 6 weeks. prior to enrollment)	N: 60 M: 0% 43 years	Tx: Deep water running 60 minutes 3x/week x 15 weeks C: Land-based exercises (walking & jogging) 60 minutes 3x/week x 15 weeks	FIQ, VAS pain, BDI, SF-36, PGART	15 weeks	Both groups improved significantly from baseline to week 15. FIQ improved more in deep water running group. No differences in improvement between groups in VAS pain, BDI, SF-36 physical and PGART. Overall attrition 13% (both groups 13%). No difference in AEs by group. Most common AE: muscle pain.
Gusi, 2010[11] Spain No funding information	Evaluate feasibility and efficacy of tilt whole-body vibration for improving dynamic balance	Body weight (post hoc)	N: 41 M: 0 53 years	Tx: Standard care plus Whole Body Vibration: three 30 minutes WBV/week x 12 weeks. (6 repetitions of 45-60 seconds 12.5Hz	Dynamic balance	3 months	Analysis limited to program completers. Participants with the heaviest weight and worst balance at baseline improved more than others ($p<0.001$). Dynamic balance of treatment

Author, Year, Country, Funder	Study Aim	Subgroup, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Subgroup Outcomes	Followup Duration	Reported Results
				vibrations per session). C: Standard care and regular daily activities			group improved by 36%; control group unchanged. No power analysis. Overall attrition 14%; 14% in treated, 10% in control group. Only 1 AE reported (pain) in treatment group participant. No AEs reported in controls.
Hakkinen, 2002[12] Finland Government & foundation funded	Effect of strength training on muscle strength and serum hormones	Premenopausal women	N: 21 M: 0 38-40 years	Tx: Supervised experimental strength training for 2 days/week x 21 weeks on weight machines C: Normal low intensity recreational activities	Isometric right knee maximal extension and flexion force; serum hormones	4 months	Maximal R knee extension and flexion forces increased significantly in the treated FM group (18% and 13% respectively). Attrition not specified in text or tables. AEs not reported.
Senna, 2012[13] (non exercise) Egypt No funding information	Effect of weight reduction on FIQ	Obese adults (*obese* criteria not defined in article)	N: 83 M: 9.6% 46 years	Tx: Dietary restriction. (1200 kcal/day (20% protein, 50% carbs,30% fat) x 6 months) C: No restriction in calories. Follow medical treatment by physician	FIQ, BDI, Sleep Quality Index, TPs	6 months	Treated group had significant change in FIQ from baseline vs. controls. Depression and sleep quality improved and TP count was reduced in weight loss group. No power calculation. Overall attrition 3% (5% treated, 2% controls). AEs not reported.
Valkeinen, 2008[14] Adjunctive to existing medications Finland Government and foundation funded	Examine effectiveness of concurrent strength and endurance training on FM symptoms	Postmenopausal women, age 50 and over	N: 26 M: 0 60 years	Tx: Strength and endurance (aerobic) training 2-4 30-60 minute sessions/week x 21 weeks at gym C: No training	Muscle strength, VO2 peak, work time, HAQ, FM symptoms	21 weeks	Muscle strength improved 2% in trained (vs.-6% in controls). Walking, stair climbing, and pain significantly improved with training; changes in fatigue, wellbeing, and sleep quality were not significantly different. Small n per group (13 tx, 11 c) and no power analysis. Overall attrition 8% (13% treated, 0% controls). AEs not reported.
Psychological							
Edinger, 2005[18] USA	Compare CBT with other behavioral therapy and usual	Insomnia 47 (100) T_1: 18 (100) T_2: 18 (100) C: 11 (100)	N: 47 T_1: 18 (38) T_2: 18 (38) C: 11 (38)	T_1: 6 weekly individual sessions 15-6 0minutes each. Audiocassette CBT module, verbal	Polysom-nography	6 months	T_1 Showed 50% reduction in nocturnal wake time, T_2 showed 20% reduction, Control group showed 2.5% reduction.

Author, Year, Country, Funder	Study Aim	Subgroup, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Subgroup Outcomes	Followup Duration	Reported Results
Government funded	care on sleep and other FM		M: 8.5% 46.5 (9.0) 50.1 (6.9)	and written stimulus control instructions + ongoing medical care T_2: 6wkly individual sessions 15-60 minutes each. Generic sleep education on audiocassette, verbal and written instructions + ongoing medical care. C: Ongoing medical care			57% of T_1 met strict subjective sleep improvement criteria, compared to 17% of T_2 and 0% of control group. Overall attrition 56% (67%=T_1, 61%=T_2, 36% controls). AEs not reported.
Scheidt, 2013[16] Germany Academic funding	Effectiveness of brief psychodynamic psychotherapy on women with FM and substantial psychological comorbidity	Sex F: 47(100) Psychological comorbidity (all): MDD: 24 (51) T: 13 (54) C: 11 (49) Dysthymia: 9 (19) T: 3 (13) C: 6 (26) Anxiety: 8 (17) T: 4 (17) C: 4 (17) Double Depression: 6 (13) T: 3 (13) C: 3 (13)	N: 47 T: 24 C: 23 M: 0 49 years	Tx: 25 weekly sessions of psychodynamic psychotherapy lasting between 50-60 minutes C: 4 primary care consultations/6months with advice on medication and exercise.	FIQ, Hospital Anxiety and depression scale, Pain disability index, Health-related QoL.	1 year	Subgroup: No significant between-group differences on primary and secondary outcome measures. Both interventions equally effective. Study not powered for subgroup treatment effect. Overall attrition 25.5% (25% in treated, 26% controls). AEs not reported.
Mixed							
Fontaine, 2010[19] USA Government funded	Evaluate effects of 30 minutes of lifestyle physical activity (a cognitive-behavioral physical activity promotion program)	Suboptimal physical activity (had not met US Surgeon General's 1996 recommended physical activity in prior 6 months)	N: 84 M: 3.6% 48 years	Tx: Lifestyle Physical Activity (LPA = a cognitive-behavioral physical activity promotion program), 6 1-hour group sessions C: FM information and support: 6 1-hour group sessions	FIQ, VAS, FSS, CES-D, TPs, 6 minute walk	3 months	Treated group increased average daily steps by 54% and had significant reductions in total FIQ and pain. Walking was the most common activity chosen. No differences in 6-minute walk, BMI, fatigue, depression or number of TPs between groups at 12 weeks. 13% dropped out (not reported

Author, Year, Country, Funder	Study Aim	Subgroup, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Subgroup Outcomes	Followup Duration	Reported Results
							by group). Baseline power to detect FIQ change was sufficient but dropouts per group were not specified. Overall attrition 13% (both groups). AEs not reported.

Abbreviations: **AE**-Adverse Effects; **BDI**-Beck Depression Inventory; **C**-Control; **CBT**-Cognitive Behavioral Therapy; **CES-D**-Center for Epidemiologic Studies Depression Scale; **FIQ**-Fibromyalgia Impact Questionnaire; **FM**-Fibromyalgia syndrome; **FSS**-Fatigue Severity Scale; **IHAD**-Iranian version of Hospital Anxiety and Depression questionnaire; **HAQ**-Health Assessment Questionnaire; **M**-Male; **MOS**-Medical Outcomes Study sleep scale; **PGART**-Patient's Global Assessment of Response to Therapy; **R**-Right; **SF-36** -MOS Short-Form 36-item Health Survey; **TPs**-Trigger Points; $\mathbf{T_x}$-Treatment group $\mathbf{T_1}$-Treatment group 1 $\mathbf{T_2}$-Treatment group 2; **VAS**-Visual Analogue Scale; $\mathbf{VO_2}$-Peak Oxygen uptake; **W**-White; **WBV**-Whole Body Vibration

Appendix Table E6. Fibromyalgia pooled studies of patient-level RCT data with subgroup reporting, by pharmacologic treatment

Author, Year, Country, Studies Pooled, Funder	Study Aim	Subgroup, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Subgroup Outcomes	Followup Duration	Reported Results
Duloxetine							
Bennett, 2012[21] USA, Puerto Rico, Germany, Spain, Sweden, UK Industry funded **Pooled**: Chappell, 2008[22] Russell, 2008[3] Arnold, 2005[4] Arnold, 2004[5]	Evaluate changes in stiffness using data pooled from 4 clinical trials	**Age** <55: 830 (62) **T_1**: 485 (64) **C**: 345 (67) **BMI** Normal: 365 (27) **T_1**: 208 (27) **C**: 157 (30) Overweight: 379 (28) **T_1**: 230 (30) **C**: 149 (29) Obese: 417 (31) **T_1**: 253 (33) **C**: 164 (32) Morbid Obesity: 103 (8) **T_1**: 62 (8) **C**: 41 (8)	N: 1,332 **T_1**: 797 **C**: 535 M: 5% 50 years	**T_1**: Either Duloxetine 60 mg or 120 mg/day x 12 weeks **C**: Placebo	FIQ (1-item Stiffness Score, 0-10 scale)	3 months	Subgroups: Treatment by age and BMI subgroup interactions not significant in FIQ stiffness change. Pooled data shown for subgroup outcome change from baseline. AEs not reported by subgroup. Overall: Statistically significant reduction in FIQ stiffness score in treated vs. controls. Reported that improvement in treated patients were above MCID (13%), but did not account for improvements in the placebo group (making the difference between treated vs. placebo to be less than MCID). No information on study power. AEs reported by treatment group, not subgroup. TEAEs differed by group (89% treated; 80% placebo). Common TEAEs were nausea, headache, dry mouth, insomnia, fatigue, GI symptoms. Note: Subgroup *n*'s do not total overall *N*.
Bradley, 2010[23] USA, Puerto Rico, Germany, Spain, Sweden, UK Industry funded **Pooled**: Chappell, 2008[22]	Assess whether fatigue/tiredness negatively associated with efficacy using data pooled from 4 clinical trials	**FIQ Tiredness** Mild (0-3): 49 (4) **T_1**: 29 (4) **C**: 20 (4) Moderate (4-6): 216 (16) **T_1**: 133 (17) **C**:83 (16) Severe (7-10): 1,067 (80) **T_1**: 634 (80)	N: 1,332 **T_1**: 797 **C**: 535 M: 5% 50 years	**T_1**: Either Duloxetine 60 mg or 120 mg/day x 1 2weeks **C**: Placebo	BPI, FIQ, PGI-I, SF-36	3 months	Subgroups: Efficacy does not vary by baseline tiredness in any outcome measure. Pooled data shown for subgroup outcomes change from baseline in all but PGI-I. Overall: Overall results not analyzed. No information on study power. AEs reported by subgroup. Nausea more common in treated patients, but

Author, Year, Country, Studies Pooled, Funder	Study Aim	Subgroup, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Subgroup Outcomes	Followup Duration	Reported Results
Russell, 2008[3] Arnold, 2005[4] Arnold, 2004[5]		**C**: 430 (80)					did not differ by subgroup. Common AEs that differed by subgroup were hypoesthesia, arthralgia, cough, and myalgia. Note: Subgroup *n*'s do not total overall *N*.
Arnold, 2009[24] USA, Puerto Rico, Germany, Spain, Sweden, UK Industry funded **Pooled**: Chappell, 2008[22] Russell, 2008[3] Arnold 2005[4] Arnold 2004[5]	Does co-morbid MDD influence efficacy and safety of duloxetine using data pooled from 4 clinical trials	**MDD**: 350 (26) **T_1**: 203 (25) **C**: 147 (27)	N : 1,332 **T_1**: 797 **C**: 535 M: 5% 50 years	**T_1**: Either Duloxetine 60 mg or 120 mg/day x 12 weeks **C**: Placebo	Primary: BPI Secondary: FIQ, CGI-S, PGI-I, HAMD, SF-36, SDS, MFI	3 months	Subgroups: KQ1: Treated patients with or without MDD had similar improvement in all outcome and safety measures. All treatment by subgroup interactions not significant. Pooled data shown. KQ2: AEs reported by subgroup. Treatment by MDD subgroup interaction for serious AEs was not significant; interaction term for treatment AEs was significant (p=0.09). Overall: Significant reduction in all outcomes in treated vs. controls. No information on study power. Most common AEs were nausea, headache, and dry mouth.
Milnacipran							
Arnold, 2012[25] USA, Canada Industry funded **Pooled**: Arnold, 2010[26] Mease, 2009[27] Clauw, 2008[28] (subgroup analysis limited to 3 of 6 trials)	Examine effect of milnacipran on changes in body weight using data pooled from 3 clinical trials	**BMI Group** <25: 711 (23) **T_1**: NR **T_2**: NR **C**: NR 25-30: 886(29) **T_1**: NR **T_2**: NR **C**: NR ≥30: 1,507 (48) **T_1**: NR **T_2**: NR **C**: NR	N: 3,014 **T_1**: NR **T_2**: NR **C**: NR M: 4% 50 years	**T_1**: Milnacipran 100 mg/day **T_2**: Milnacipran 200 mg/day x 12 weeks **C**: Placebo	Change in Body Weight	3 months	Subgroups: Treated patients who were overweight/obese had greater mean weight loss than normal/underweight patients. No formal statistical comparisons were done. Pooled data shown. AEs not reported by subgroup. Overall: Treated patients lost significantly more weight than controls, regardless of baseline BMI. No information on study power. AEs reported by treatment group, but not by

Author, Year, Country, Studies Pooled, Funder	Study Aim	Subgroup, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Subgroup Outcomes	Followup Duration	Reported Results
							subgroup. Most common AE was nausea.
Geisser, 2011[29] USA Industry funded **Pooled**: Mease, 2009[27] Clauw, 2008[28]	Determine whether improvements in pain measures are dependent on baseline pain severity	**Median VAS Pain** ≤64.7: UTD **T_1**: UTD **T_2**: UTD **C**: UTD >64.7: UTD **T_1**: UTD **T_2**: UTD **C**: UTD	N: 2,084 **T_1**: 624 **T_2**: 623 **C**: 837 M: 4% 50 years	**T_1**: Milnacipran 100 mg/day **T_2**: Milnacipran 200 mg/day x 12 weeks **C**: Placebo	Treatment efficacy: VAS, PGIC, SF-36 (Physical) Note: Efficacy defined a priori as 2-measure or 3-measure composite responder. Each scale also analyzed separately.	3 months	Subgroups: Similar % of treated patients met composite responder criteria vs placebo, regardless of pain severity. Significantly higher % of treated patients with low to moderate pain severity had improvements in physical functioning vs placebo. Pooled data shown. Overall: Significantly higher % of treated patients met the composite responder criteria vs. controls. No information on study power. AEs reported by treatment group, but not by subgroup. Most common AEs were nausea, headache, constipation, insomnia. Note: *n* in VAS pain groups changed depending on outcome measure analyzed.
Pregabalin							
Arnold, 2010[30] USA Industry funded **Pooled**: Arnold, 200[31] Mease, 2008[32] Crofford, 2005[33]	Evaluate changes in pain and symptoms of anxiety and depression using data pooled from 3 clinical trials	**Change in Anxiety and Depression** Anxiety ≥2 pts: 939 (47) **T_1**: 62 (47) **T_2**: 232 (46) **T_3**: 243 (49) **T_4**: 181 (48) **C**: 221 (44) Depression ≥2 pts: 806 (40) **T_1**: 56 (43) **T_2**: 203 (41) **T_3**: 207 (41) **T_4**: 159 (42) **C**: 181 (36)	N: 2,013 **T_1**: 131 **T_2**: 500 **T_3**: 501 **T_4**: 378 **C**: 503 M: 5% 49 years	**T_1**: Pregabalin 150 mg/day **T_2**: Pregabalin 300 mg/day **T_3**: Pregabalin 450 mg/day **T_4**: Pregabalin 600 mg/day x 12 weeks **C**: Placebo	Weekly Mean Pain Diary Score (11 point scale)	8-14 weeks	Subgroups: Change in pain score did not depend on changes in anxiety or depression. Pooled data shown. Overall: Except for lowest dose, significant reduction in pain score in treated vs. placebo. Power discussed only generally. No AEs reported (overall or subgroup).

Author, Year, Country, Studies Pooled, Funder	Study Aim	Subgroup, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Subgroup Outcomes	Followup Duration	Reported Results
Bhadra, 2010[34] USA, Canada, Mexico, Denmark, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, UK, India, Korea, Australia, Venezuela Industry funded **Pooled**: Arnold, 2008[31] Mease, 2008[32] Crofford, 2005[33] Pauer, 2008[35]	Evaluate efficacy in patients with co-morbid conditions using data pooled from 4 clinical trials	**By 11 conditions** Headache: 970 (37) Immune disorder: 967 (37) GI reflux: 683 (26) Insomnia: 657 (25) Depression: 618 (24) IBS: 509 (20) Neurological: 469 (18) Asthma: 323 (12) Anxiety: 228 (9) Restless legs (RLS): 65 (3)	N: 2,624 **T_1**: 686 **T_2**: 686 **T_3**: 563 **C**: 689 M: NR 49 years	**T_1**: Pregabalin 300 mg/day **T_2**: Pregabalin 450 mg/day **T_3**: Pregabalin 600 mg/day x 12 weeks **C**: Placebo	Weekly Mean Pain Diary Score (11 point scale), PGIC	8-12 weeks	Subgroups: Change in pain score and PGIC did not vary by comorbid medical condition. Pooled data shown. Overall: Significant improvements in mean pain score and PGIC in treated vs placebo. No information on study power. No AEs reported (overall or subgroup). Note: Comorbid conditions not mutually exclusive
Byon, 2010[36] USA, Canada, Mexico, Denmark, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, UK, India, Korea, Australia, Venezuela Industry funded **Pooled**: Arnold, 2008[31]	Describe exposure-response relationship, and examine potential subgroup differences using data pooled from 4 clinical trials	**Age** <40: 534 (19) 40-60: 1,830 (66) >60: 395 (14) **Sex** F: 2,568 (93)	N: 2,759 **T_1**: NR **T_2**: NR **T_3**: NR **T_4**: NR **C**: NR M = 7% 49 years	**T_1**: Pregabalin 150 mg/day **T_2**: Pregabalin 300 mg/day **T_3**: Pregabalin 450 mg/day **T_4**: Pregabalin 600 mg/day x 12 weeks **C**: Placebo	Treatment Response: Weekly Mean Pain Diary Score (11 point scale), PGIC	8-14 weeks	Subgroups: Study reports greater pain reduction in older versus younger patients and in females vs. males. Statistical modeling paper with insufficient information on actual (vs. predicted) clinical values to evaluate changes from baseline Overall: Exposure-response models were developed to describe the relationship between pregabalin and reductions in pain and improvements in PGIC. No information on study power. No AEs reported (overall or subgroup).

Author, Year, Country, Studies Pooled, Funder	Study Aim	Subgroup, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Subgroup Outcomes	Followup Duration	Reported Results
Mease, 2008[32] Crofford, 2005[33] Pauer 2008[35]							

Abbreviations: **AEs**-adverse effects; **BMI**-Body Mass Index;-**BPI**-Brief Pain Inventory; **C**-Control; **CGI-S**-Clinical Global Impression of Severity Scale; **F**-Female; **FIQ**-Fibromyalgia Impact Questionnaire; **HAMD**-Hamilton Rating Scale for Depression; **M**-Male; **MDD**-Major Depressive Disorder; **MFI**-Multidimensional Fatigue Inventory; **PGI-I**-Patient Global Impression of Improvement Scale; **PGIC**-Patient Global Impression of Change Score; **SAEs**- serious adverse events per authors; **SDS**-Sheehan Disability Scale; **SF-36**-Short-Form Health Survey; $\mathbf{T_x}$-Treatment group $\mathbf{T_1}$-Treatment group 1 $\mathbf{T_2}$-Treatment group 2; **TEAEs**- treatment-emergent adverse events per authors; **VAS**-Visual Analog Scale 24-hour recall pain score

Appendix Table E7. Fibromyalgia observational studies with subgroups, by class of treatment

Author, Year, Country, Funder	Study Aim Study Design	Subgroup*, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Subgroup Outcomes	Followup Duration	Reported Results
Pharmacologic							
Arnold, 2012[37] USA, Canada Industry funded (Connected to RCT: Arnold 2010)	Post hoc examination of relationships among pain, depressive symptoms and global status in patients taking milnacipran Patients who met criteria for MDD excluded from trial; patients in study may have experienced depressive symptomology rather than satisfied criteria for MDD	**BDI** <10: 599 (58) **T_1**: 294 (57) **C**: 305 (60) 10-18: 317 (31) **T_1**: 168 (33) **C**: 149 (29) 19-25: 109 (11) **T_1**: 54 (10) **C**: 55 (11) **BDI Change** >4: 289 (28) **T_1**: NR **C**: NR ≤4: 291 (28) **T_1**: NR **C**: NR No improvement/ worse: 445 (43) **T_1**: NR **C**: NR	N: 1,025 **T_1**: 516 **C**: 509 M: 5% 49 years	**T_1**: Milnacipran 100mg/day x 12 weeks **C**: placebo	Pain responder: ≥30% VAS improvement PGIC responder: rates overall change as 1 or 2 2-measure composite responder: Met both criteria	3 months	Subgroups: Pain reduction among treated weakly associated with baseline depressive symptoms. Improvements largely independent of improvements in depressive symptomology. No formal statistical subgroup analysis performed. Subgroup attrition not reported. AEs not reported by subgroup Overall: Significantly greater reduction in mean pain scores and lower mean PGIC in treated vs controls. No information on study power. Overall attrition not reported AEs not reported.
Younger, 2009[38] USA Nonprofit/ foundation funded	Determine effectiveness of low-dose naltrexone and whether BL characteristics predict treatment response Single-blind crossover trial	**ESR** Subgroups NR	N: 10 **T_1**: 10 **C**: 10 M: 0% 44 years	**T_1**: Naltrexone 4.5 mg/day x 8 weeks **C**: placebo x 2 weeks	VAS Clinical Significance Threshold: 30% reduction in symptoms over placebo	14 weeks	Subgroups: Greater pain reduction in treated among those with elevated ESR. Subgroup attrition not reported. AEs not reported by subgroup Overall: Significantly greater reduction in pain in treated vs placebo. Study powered to find 30% reduction in symptoms. Overall attrition 16.7%. Common AEs were vivid dreams, nausea, insomnia.
Physical							
Drexler, 2002[39] Austria	Determine efficacy of EMG-biofeedback by MMPI score	**MMPI** 24 (100) **Group 1:** Psychologically	N: 24 **T_1**: 12 **C**: 12 M: 0%	**Group 1**: Biofeedback therapy as an EMG-reduction training, 2 45-minute	Pressure Point Score, Pain Perception	3 months	Subgroups: Psychologically abnormal MMPI (Group 1) patients experienced improvements in all measured

Author, Year, Country, Funder	Study Aim Study Design	Subgroup*, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Subgroup Outcomes	Followup Duration	Reported Results
Funding not reported		Abnormal: 12 (50) **Group 2**: Psychologically Normal: 12 (50)	50 years	sessions/week x 6 weeks **Group 2:** same intervention	Scale, SF-36		parameters (symptoms, sensory, and affective pain components, QOL). Group 2 (psychologically normal MMPI) patients experienced improvements only in pressure point sensitivity, vitality, and mental health. Group 1 patients were much worse off at baseline in all measures. Subgroup attrition not reported. AEs not reported by subgroup Overall: Long-term improvement only in pressure point sensitivity and sensory pain dimensions. No information on study power. Overall attrition not reported. AEs not reported.
Mixed							
Joshi, 2009[40] India No funding	Compare physiotherapy and amitriptyline, and determine whether BL characteristics predict treatment benefit	**FIQ Pain Score** >50: NR ≤50: NR **SES** Low: 82(47) T_1: 42(48) T_2: 40(45)	N: 175 T_1: 87 T_2: 88 M: 5% 39 years	T_1: Amitriptyline 25 mg/day x 6 months, titrated to 50 mg/day if no benefit seen T_2: Physiotherapy daily, step-up exercise pattern starting at 2 times, 10 minutes/day. Exercise followed by relaxation, stretching, strengthening	FIQ Benefit defined as: ≥2 SD reduction in FIQ score over 6 months	6 months	Subgroups: Low SES and high FIQ score at baseline were only factors that predicted benefit from either therapy. Subgroup attrition not reported. AEs not reported by subgroup Overall: Both strategies significantly reduced disability and were equally effective. No information on study power. Overall attrition not reported. AEs not reported

Abbreviations: **AE**-adverse effect; **BDI**-Beck Depression Inventory, **C**-Control; **ESR**-erythrocyte sedimentation rate, **FIQ**- Fibromyalgia Impact Questionnaire, **M**-Male; **MMPI**-Minnesota Multiphasic Personality Inventory, **NR**-Not Reported; **PGIC**-Patient Global Impression of Change Score; **SES**-socioeconomic status; T_x-Treatment group T_1-Treatment group 1 T_2-Treatment group 2; **VAS**-Visual Analog Scale 24-hour recall pain score

* Determined at baseline unless otherwise noted

Appendix Table E8. Outcomes assessed in the fibromyalgia randomized clinical trial literature, by patient subgroup

Outcome	Articles in Which Outcome was Used and for Which Subgroups
Overall Pain	
Visual Analog Scale (VAS) for pain	d: Gendreau, 2005[6] j: Sadreddini, 2008[9]; Assis, 2006[10]; Fontaine, 2010[19]
Brief Pain Inventory	a: Russell, 2008[3]; Arnold, 2012[1] b: Arnold, 2005[4]; Russell, 2008[3]; Arnold, 2012[1] c: Arnold, 2012[1]; Russell, 2008[3] d: Arnold, 2005[4]; Arnold, 2012[1]; Russell, 2008[3]
McGill Pain Questionnaire	d: Gendreau, 2005[6] Arnold, 2002[7]
Tender point (TP) assessments	a: Russell, 2008[3] b: Russell, 2008[3]; Arnold, 2004[5] c: Russell, 2008[3] d: Russell, 2008[3]; Arnold, 2002[7]; Arnold, 2004[5]; Arnold, 2005[4] e: Senna, 2012[13] j: Sadreddini, 2008[9]; Fontaine, 2010[19]
E-diary pain score	d: Gendreau, 2005[6]
Modified pain map	j: Stenning, 2011[8]
Gracely pain scale	d: Gendreau, 2005[6]
Fibromyalgia Symptom Improvement	
Fibromyalgia Impact Questionnaire (FIQ)	a: Arnold, 2012[1]; Russell, 2008[3] b: Arnold, 2012 [1]; Arnold, 2004[5]; Russell, 2008[3] c: Arnold, 2012 [1]; Russell, 2008[3] d: Arnold, 2002[7]; Arnold, 2004[5]; Arnold, 2005[4]; Arnold, 2012 [1], Scheidt, 2013[16] ; Russell, 2008[3] e: Senna, 2012[13] f: Lera, 2009[20] j: Assis, 2006[10]; Fontaine, 2010[19]
Symptom Checklist-90-Revised (SCL-90-R)	f: Lera, 2009[20]
Patient Global Impression of Improvement (PGI-I)	a: Arnold, 2010[2]; Arnold, 2012 [1] ; Russell, 2008[3] b: Arnold, 2010[2]; Arnold, 2012[1]; Russell, 2008[3]; Arnold, 2004[5] c: Arnold, 2010 [2]; Arnold, 2012 [1]; Russell, 2008[3] d: Arnold, 2004[5]; Arnold, 2005[4]; Arnold, 2010[2]; Arnold, 2012[1]; ussell, 2008[3]
Clinical Global Impression of Severity Scale (CGI-S)	a: Russell, 2008[3] b: Russell, 2008[3]; Arnold, 2004[5] c: Russell, 2008[3] d: Russell, 2008[3]; Arnold, 2004[5]; Arnold, 2005[4]
Function	
Sheehan Disability Scale	a: Russell, 2008[3] b: Russell, 2008[3]; Arnold, 2004[5] c: Russell, 2008[3] d: Russell, 2008[3]; Arnold, 2004[5]; Arnold, 2005[4]
6 minute walk	j: Fontaine, 2010[19]
Isometric strength testing	j: Hakkinen, 2001[41]
Muscle strength	j: Valkeinen, 2008[14]
Dynamic balance	e: Gusi, 2010[11]

Outcome	Articles in Which Outcome was Used and for Which Subgroups
Participation	
Work time	j: Valkeinen, 2008[14]
Health-Related Quality of Life	
Medical Outcomes Study Short-form 36-item Health Survey (SF-36)	a: Russell, 2008[3] b: Russell, 2008[3]; Arnold, 2004[5] c: Russell, 2008[3] d: Russell, 2008[3]; Arnold, 2004[5]; Arnold, 2005[4] f: Lera, 2009[20] j: Assis, 2006[10]
Fatigue	
Fatigue Severity Scale (FSS)	j: Fontaine, 2010[19]
Multidimensional Fatigue Inventory (MFI)	a: Russell, 2008[3] b: Russell, 2008[3] c: Russell, 2008[3] d: Russell, 2008[3]
Sleep Quality	
Polysomnography	j: Edinger, 2005[18]
The Pittsburgh Sleep Quality Index (PSQI)	e: Senna, 2012[13]
Sleep Disturbance	j: Sadreddini, 2008[9]
Depression and/or Anxiety	
Beck Depression Inventory(BDI) (Beck 1996)	b: Arnold, 2004[5] d: Arnold, 2004[5] e: Senna, 2012[13] j: Assis, 2006[10]
Hospital Anxiety and Depression Scale	d: Scheidt, 2013[16]
Hospital Anxiety and Depression Questionnaire, Iranian version (IHAD)	j: Sadreddini, 2008[9]
Quantitative Sensory testing	j: Stenning, 2011[8]
Hamilton Rating Scale of Depression (HAMD)	a: Russell, 2008[3] b: Russell, 2008[3] c: Russell, 2008[3] d: Russell, 2008[3]; Arnold, 2005[4]
Center for Epidemiologic Studies Depression Scale (CES-D)	j: Fontaine 2010[19]
Depression Quality of Life	d: Arnold, 2005[4]; Scheidt, 2013[16]
Health status	
EuroQol (EQ-5D)	a: Russell, 2008[3] b: Russell, 2008[3] c: Russell, 2008[3] d: Russell, 2008[3]
Composite measure of pain, fatigue, and psychological well-being	j: Junghaenel, 2008[15]
Health Assessment Questionnaire (HAQ)	j: Sadreddini, 2008[9]; Valkeinen, 2008[14]
Patient's Global Assessment of Response to Therapy	j: Assis, 2006[10]
Other outcomes	
VO_2 (peak oxygen uptake)	j: Valkeinen, 2008[14]
Serum hormone levels	j: Hakkinen, 2001[41]

a=age; b=sex; c=race d=any Mental Health condition; e=obesity; f=fatigue; h= other chronic pain condition(s); j=other subgroup

Appendix Table E9. Outcomes assessed in pooled randomized clinical trial analyses and observational studies by subgroup

Outcome	Number of Articles	Articles in Which Outcome was Used and for Which Subgroups
Pooled analyses of patient-level randomized clinical trial data		
Overall Pain		
Brief Pain Inventory (BPI)	2	d: Arnold, 2009[24] j: Bradley, 2010[23]
Fibromyalgia Impact Questionnaire	2	d: Arnold, 2009[24] j: Bradley, 2010[23]
Visual Analog Scale (VAS) for pain	1	j: Geisser, 2011[29]
Weekly Mean Pain Dairy Score	3	d: Arnold, 2010[30] f: Bhadra, 2010[34] a: Byon, 2010[36] b: Byon, 201 [36]
Fibromyalgia Symptom Improvement		
Clinical Global Impression of Severity Scale (CGI-S)	1	d: Arnold, 2009[24]
Patient Global Impression of Change (PGI-C)	1	j: Geisser, 2011[29] f: Bhadra, 2010[34] a: Byon, 2010[36] b: Byon, 2010[36]
Patient Global Impression of Improvement (PGI-I)	2	d: Arnold, 2009[24] j: Bradley, 2010[23]
Function		-
FIQ subscale: stiffness item	1	a: Bennett, 2012[21] e: Bennett, 2012[21]
Sheehan Disability Scale (SDS)	1	d: Arnold, 2009[24]
Participation		None
Health-Related Quality of Life		
Medical Outcomes Study Short-form 36-item Health Survey (SF-36)	3	d: Arnold, 2009[24] j: Bradley, 2010[23] j: Geisser, 2011[29]
Fatigue		
Multidimensional Fatigue Inventory (MFI)	1	d: Arnold, 2009[24]
Sleep Quality		-
Other outcomes		
Depression		
Hamilton Depression Rating Scale (HAMD)		d: Arnold, 2009[24]
Obesity-Related		
Change in Body Weight	1	e: Arnold, 2012[25]
Observational studies		
Overall Pain		
FIQ subscale: pain item	1	j: Joshi, 2009[40]
Pain Perception Scale	1	j: Drexler, 2002[39]

Pressure Point Sensitivity	1	j: Drexler, 2002[39]
Visual Analog Scale (VAS) for pain	2	d: Arnold, 2012[37] j: Younger, 2009[38]
Fibromyalgia Symptom Improvement		
Patient Global Impression of Change (PGI-C)	1	d: Arnold, 2012[37]
Health-Related Quality of Life		
Short-form 36-item Health Survey (SF-36)	1	j: Drexler, 2002[39]

Subgroup Key, Protocol Defined Subgroups: a=age; b=sex; c=high FM severity; d=any Mental Health; e=obesity; f=non-rheumatologic medical comorbidities; g= rheumatologic comorbidity; h= other chronic pain condition(s); i=longer FM duration; j=other subgroup (not defined in protocol)

Appendix Table E10. Fibromyalgia risk of bias summary for RCTs: mixed samples and pure subgroups

Study	Overall Risk of Bias Assessment	Rationale
MIXED SAMPLES		
Pharmacologic		
Duloxetine		
Arnold, 2012[1]	High	High attrition, subgroup attrition not separately identified, small subgroup sample size, powered to detect main not subgroup effects
Arnold, 2010[2]	High	High attrition, subgroup attrition not separately identified, small subgroup sample size, powered to detect main not subgroup effects
Russell, 2008[3]	High	High attrition, subgroup attrition not separately identified, small subgroup sample size, powered to detect main not subgroup effects, table denominators reflect baseline not followup numbers of patients, drop-outs assigned a score of no change for one primary outcome in analyses.
Arnold, 2005[4]	High	High attrition, subgroup attrition not separately identified, subgroup sample size within treatment group not specified, powered to detect main not subgroup effects
Arnold, 2004[5]	High	High attrition, subgroup attrition not separately identified, small subgroup sample size in some instances, though authors argue study adequately powered to detect subgroup effect, power calculations based on main and not subgroup effect, selective outcome reporting.
Milnacipran		
Gendreau, 2005[6]	High	High attrition, subgroup attrition not separately identified, small subgroup sample size, no information on study power, no adjustment for multiple comparisons, incomplete outcomes reporting for subgroup analysis
Off-label		
Arnold, 2002[7]	High	High attrition, subgroup attrition not separately identified, small subgroup sample size, no information on study power, subgroup analysis not specified a priori
Psychological		
Junghaenel, 2008[15]	High	Small sample size, no blinding mentioned, no randomization detail given not powered for either main outcomes or subgroup effect
Mixed		
Lera, 2009[20]	High	High attrition, subgroup attrition not separately identified, small subgroup sample size, study not powered for either main outcome or subgroup effect, subgroup not determined a-priori, inadequate blinding
PURE SUBGROUPS		
Pharmacologic		
Off-label		
Stening, 2011[8]	High	Small sample size, not powered, no randomization detail given, double-blinded, low attrition, larger proportion of subjects in placebo group on anti-depressants.
Sadreddini, 2008{Sadreddini, 2008	High	Nature of treatment precludes blinding, no adjustment for multiple comparisons, outcomes assessors not blinded, low attrition, study powered for main outcome, no details on how randomization carried out
Physical		

Study	Overall Risk of Bias Assessment	Rationale
Assis, 2006[10]	Moderate	Nature of treatment precludes blinding, no adjustment for multiple comparisons, lacking detail on blinding of outcome assessors and permitted co-interventions Low attrition (<15%, same in each group), blinded patients and investigators to the extent possible for type of intervention, study adequately powered to detect difference in primary outcome
Gusi, 2010[11]	Moderate	Nature of treatment precludes full blinding, post-hoc defined subgroups, subgroup sample size not reported and small sample size overall, no information on study power, and no adjustment for multiple comparisons Low attrition (<15%, similar in each group), blinded patients and study staff to the extent possible for type of intervention
Hakkinen, 2002[12]	High	No randomization details, not powered for main outcome, no binding, no inclusion/exclusion criteria stated, small sample size
Senna, 2012[13]	High	Small sample size, study not powered for main outcome, researchers not blinded to intervention due to nature of the study though outcomes assessors were blinded, randomization process not detailed ("concealed envelope method, block size of 4). Low attrition.
Valkeinen, 2008[14]	High	Randomization process not detailed, small sample size, no blinding, no power analysis
Psychological		
Edinger, 2005[18]	High	Small sample size, no power analysis, subjects and researchers not blinded, randomization process not specified
Scheidt, 2013{Scheidt, 2013 #4489	High	Randomization process not specified ("randomized into groups by blocks of 10), inadequate blinding (of evaluators) but outcomes were self-report questionnaires, sufficient power and sample size, >20% attrition, no information on baseline characteristics of drop-outs. Sufficient power and sample size.
Mixed		
Fontaine, 2010[19]	High	High attrition rate, randomization process not detailed, no blinding, interventions not easily replicable, study powered for main outcome

Appendix Table E11. Fibromyalgia risk of bias summary for observational studies

Study	Overall Risk of Bias Assessment	Rationale
Pharmacologic		
Arnold, 2012[37]	High	No information on study power, other variables that might have influenced outcome not taken into consideration (e.g., fatigue), subgroups not clearly defined (Hints at "Comorbid depression," but not adequately measured).
Younger, 2009[38]	High	Subgroup N not reported, subjects used as self-control so no randomization, no meaningful comparison between placebo and intervention, small total sample size (n=20) though powered for main effect, single-blinded
Psychological		
Drexler, 2002[39]	High	Small sample size, no information on study power, self-controls (quasi-experimental design), uncertain blinding, significant differences in all baseline characteristics between groups
Mixed		
Joshi, 2009[40]	High	Small sample size, no randomization detail given, patients lost to followup not described, significant difference (p=0.04) in a parameter in baseline characteristics, no information on study power.

Appendix Table E12: Quality issues and risk of bias summary for pooled analyses of patient-level randomized clinical trial data on fibromyalgia subgroups

Study	Pooled RCTs	Overall Risk of Bias Assessment	Rationale
Pharmacologic (all)			
Duloxetine			
Bennett, 2012[21]	Chappell, 2008[22] Russell, 2008[3] Arnold, 2005[4] Arnold, 2004[5]	RCT inputs: High Pooled: issues detailed in rationale	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, outcome measure is subscale of common tool but subscale has not been formally validated, study power not discussed, no adjustments made for multiple comparisons and less stringent statistical criteria used to evaluate treatment-by-subgroup interaction, attrition not discussed despite high attrition in input RCTs, small sample size in certain subgroup strata (e.g., extreme obesity) Used optimal individual patient data (IPD) pooled analytic technique (Fischer et al. 2011)[42] study blinding input RCTs: High risk of bias (all 4 studies)
Bradley, 2010[23]	Chappell, 2008[22] Russell, 2008[3] Arnold, 2005[4] Arnold, 2004[5]	RCT inputs: High Pooled: issues detailed in rationale	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, study power not discussed, no adjustments for multiple comparisons and less stringent statistical criteria used to evaluate treatment-by-subgroup interactions, attrition not discussed despite high attrition in input RCTs, some selective reporting in results presentation, small sample size in certain subgroup strata (e.g., FIQ tiredness, mile group), different duloxetine doses combined analysis (with rationale) Used optimal individual patient data (IPD) pooled analytic technique (Fischer et al. 2011)[42] study blinding input RCTs: High risk of bias (all 4 studies)
Arnold, 2009[24]	Chappell, 2008[22] Russell, 2008[3] Arnold, 2005[4] Arnold, 2004[5]	RCT inputs: High Pooled: issues detailed in rationale	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, study power not discussed, no adjustments for multiple comparisons and less stringent statistical criteria used to evaluate treatment-by-subgroup interactions, attrition not discussed despite high attrition in input RCTs, some selective reporting in results presentation, different duloxetine doses combined analysis (with rationale) Used optimal individual patient data (IPD) pooled analytic technique (Fischer et al. 2011)[42] study blinding input RCTs: High risk of bias (all 4 studies)
Milnacipran			
Arnold, 2012[25]	Subgroup analysis: Arnold, 2010[26]	RCT inputs: High	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, study power not discussed, no adjustments for multiple

Study	Pooled RCTs	Overall Risk of Bias Assessment	Rationale
	Mease, 2009[27] Clauw, 2008[28]	Pooled: issues detailed in rationale	comparisons, attrition not discussed despite high attrition in input RCTs, unable to determine subgroup sample size within each treatment group Used optimal individual patient data (IPD) pooled analytic technique (Fischer et al. 2011)[42] study blinding input RCTs: High risk of bias (all 3 input studies)
Geisser, 2011[29]	Mease, 2009[27] Clauw, 2008[28]	RCT inputs: High Pooled: issues detailed in rationale	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, study power not discussed, no adjustments for multiple comparisons, attrition not discussed despite high attrition in input RCTs, unable to determine subgroup sample size, only patients classified as responders included in subgroup analyses Used optimal individual patient data (IPD) pooled analytic technique (Fischer et al. 2011){Fisher, 2011 #4632{ study blinding input RCTs: High risk of bias (both input studies)
Pregabalin			
Arnold, 2010[30]	Arnold, 2008[31] Mease, 2008[32] Crofford, 2005[33]	RCT inputs: High Pooled: issues detailed in rationale	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, study power not discussed, no adjustments made for multiple comparisons, outcome assessment timing varies by study, attrition not discussed despite high attrition in input RCTs, unable to determine effect of treatment in subgroups as reported Used optimal individual patient data (IPD) pooled analytic technique (Fischer et al. 2011)[42] study blinding input RCTs: High risk of bias (all)
Bhadra, 2010[34]	Arnold, 2008[31] Mease, 2008[32] Crofford, 2005[33] Pauer, 2008[35]	RCT inputs: High Pooled: issues detailed in rationale	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, study power not discussed, no adjustments made for multiple comparisons, outcome assessment timing varies by study, attrition not discussed despite high attrition in input RCTs, only those with given co-morbid medical condition are shown in results and not those without Used optimal individual patient data (IPD) pooled analytic technique (Fischer et al. 2011)[42], study blinding input RCTs: High risk of bias (3 of 4 studies, 4th study unable to determine; Pauer et al. is an abstract only)
Byon, 2010[36]	Arnold, 2008[31] Mease, 2008[32] Crofford, 2005[33]	RCT inputs: High Pooled: issues detailed in rationale	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, study power not discussed, outcome assessment timing varies by study, attrition not discussed despite high attrition in input RCTs,

Study	Pooled RCTs	Overall Risk of Bias Assessment	Rationale
	Pauer 2008[35]		insufficient information on actual (vs. predicted) clinical values to evaluate changes from baseline in subgroups input RCTs: High risk of bias (3 of 4 studies, 4th study unable to determine; Pauer et al. is an abstract only – unable to assess quality)

Appendix Table E13. Funding source and corresponding author information in fibromyalgia randomized clinical trials, mixed samples

Author, Year	Funding Source*	Corresponding/ author information
Pharmacologic		
Duloxetine		
Arnold, 2012[1] *Safety & Efficacy*	Eli Lilly & Company	Corresponding author not listed. Reprints addressed to industry author (Eli Lilly & Company). Two of three authors were full time employees and stockholders in the company; third author received grants and was a company consultant.
Arnold, 2010[2] *Flexible Dosed Duloxetine*	Funding source not reported. ClinicalTrials.gov listed sponsor as Eli Lilly & Company; collaborator as Boehringer Ingelheim	Industry author (Eli Lilly & Company)
Russell, 2008[3]	Eli Lilly & Company and Boehringer Ingelheim	Industry author (Lilly Research Laboratories) with joint appointment in the Indiana University School of Medicine
Arnold, 2005[4] *Duloxetine*	Eli Lilly & Company	Academic (no conflict of interest information provided). Of six authors, four were employees at Eli Lilly; two were in academics (one also worked as a consultant).
Arnold, 2004[5] *Duloxetine MDD*	Eli Lilly & Company. Clinical Operations staff and Statistical Analyst group of the Cymbalta product team implemented trial and provided statistical programming support	Academic (received consulting fees or honoraria in excess of $10,000 in the prior 2 years from Eli Lilly and Co). Of seven authors, three were employees of Eli Lilly, one had an appointment at two academic centers and was an employee of Eli Lilly, and one was at an academic institution but also worked as a consultant.
Milnacipran		
Gendreau, 2005[6]	Supported by Cypress Biosciences	Corresponding author not listed. Reprints addressed to industry author (Cypress Biosciences). Of ten authors, three were employees of Cypress Biosciences, three were paid consultants and shareholders, and two were consultants.
Off-label		
Arnold, 2002[7] *Fluoxetine*	Investigator-initiated grant from Eli Lilly & Company	Corresponding author not listed, reprints addressed to academic author
Psychological		
Junghaenel, 2008[15]	Supported by Rheumatology Health Professional Investigator Award from the American College of Rheumatology Research & Education Foundation. Material support provided by Applied Behavioral Medicine Research Institute, Stony Brook University	Academic
Mixed		
Lera, 2009[20]	Funding source not reported	Academic

* Information obtained from article unless otherwise noted

Appendix Table E14. Funding source and corresponding author information in fibromyalgia randomized clinical trials, pure subgroup samples

Author, Year	Funding Source*	Corresponding Author
Pharmacologic		
Off-label		
Stening, 2011[8]	Swedish Research Council – Medicine, the Swedish Brain Foundation, the Health Research Council (SE Sweden) and the Linnaeus University.ClinicalTrials.gov listed sponsor as Ostergotland County Council, Sweden	Academic
Sadreddini, 2008[9]	Funding source not reported	Academic
Physical		
Assis, 2006[10]	Grant from FAPESP, the Research Support Fund of the State of São Paulo	Academic
Gusi, 2010[11]	Funding source not reported	Academic
Hakkinen, 2002[12]	Supported in part by grants from the Finnish Social Insurance Institution and the Yrjö Jahnsson Foundation	Corresponding author not listed; reprints addressed to academic author
Senna, 2012[13]	Funding source not reported	Corresponding author not stated; academic contact provided.
Valkeinen, 2008[14]	Ministry of Education of Finland and the Peurunka-Medical Rehabilitation Foundation, Laukaa, Finland	Corresponding author not listed; reprints addressed to academic author
Psychological		
Edinger, 2005[18]	Federal grant (R21) from NIH/National Institute of Arthritis and Musculoskeletal & Skin Diseases	Academic, Veterans Affairs Medical Center
Scheidt, 2013[16]	Supported as part of an Interdisciplinary Research Project by the Freiburg Institute of Advance Studies (FRIAS)	Academic
Fontaine, 2010[19]	Federal grant, NIH/National Institute of Arthritis and Musculoskeletal & Skin Diseases	Academic

* Information obtained from article unless otherwise noted

Appendix Table E15. Funding source and corresponding author information in fibromyalgia pooled studies of individual patient data from randomized clinical trials

Author, Year	Funding Source*	Corresponding Author
Arnold, 2009[24]	Eli Lilly and Co.	Industry: Lilly Research Labs, Eli Lilly and Co.
Arnold. 2010[30] Pregabalin	Pfizer Inc., USA.	Academic (also received consultation fees from Cypress Biosciences, Forest Lab, AstraZeneca, Eli Lilly and Co., Pfizer, Boehringer Ingelheim, Allergan). Three other authors were employees of Pfizer.
Arnold, 2012[25] Milnacipran	Forest Laboratories Inc. and Forest Research Institute Inc.	Academic (also received consultation fees from Cypress Biosciences, Forest Lab, AstraZeneca, Eli Lilly and Co., Pfizer, Boehringer Ingelheim, Allergan, etc.)
Bennett, 2012[21]	Eli Lilly and Company	Academic (also received consulting fees from Eli Lilly). Two authors were employees and stockholders of Eli Lilly and Company.
Bhadra, 2010[34]	Pfizer Inc.	Industry. Authors were employees of Pfizer
Bradley, 2010[23]	Eli Lilly and Company and Boehringer Ingelheim, Inc.	Academic (also a consultant for Eli Lilly and Co, Pfizer and Forest Laboratories Inc.). Two authors work on industry advisory boards and one had been paid as a consultant and speaker for Pfizer, Eli Lilly & Co, Forest laboratories, etc.
Byon, 2010[36]	Pfizer Inc.	Industry. Authors were full-time employees of Pfizer Inc.
Geisser, 2011[29]	Forest Laboratories Inc.	Academic (also vice president, chief medical director, and shareholder at Cypress Biosciences Inc., and had received research grant support from Cypress Biosciences). One author was a senior medical director at Forest Research Institute, one was a full time employee at Forest Research Institute and one author was an academic who served as a consultant and had received grant support from Cypress Biosciences.

Appendix Table E16. Funding source and corresponding author information in fibromyalgia observational studies

Author, Year	Funding Source*	Corresponding Author
Arnold, 2012[37]	Forest laboratories Inc. and Pfizer Inc.	Academic (had received consultation fees from Cypress Biosciences, Forest Lab, AstraZeneca, etc.) Two authors were full-time employees of Forest Laboratories Inc.
Drexler, 2002[39]	Funding source not reported.	Academic
Joshi, 2009[40]	No funding. No conflict of interest declared.	Academic (declared no conflict of interest)
Younger, 2009[38]	Supported by American Fibromyalgia Syndrome Association, Oxnard Foundation (nonprofit) and Arthritis Foundation, and private contributions	Academic

References for Appendix E. Evidence Tables

1. Arnold LM, Zhang S, Pangallo BA. Efficacy and safety of duloxetine 30 mg/d in patients with fibromyalgia: a randomized, double-blind, placebo-controlled study. Clin J Pain 2012; Nov-Dec;28(9):775-81. PMID: 22971669.
2. Arnold LM, Clauw D, Wang F, et al. Flexible dosed duloxetine in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. J Rheumatol 2010; Dec;37(12):2578-86. PMID: 20843911.
3. Russell IJ, Mease PJ, Smith TR, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. Pain 2008; Jun;136(3):432-44. PMID: 18395345.
4. Arnold LM, Rosen A, Pritchett YL, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain 2005; Dec 15;119(1-3):5-15. PMID: 16298061.
5. Arnold LM, Lu Y, Crofford LJ, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis Rheum 2004; Sep;50(9):2974-84. PMID: 15457467.
6. Gendreau RM, Thorn MD, Gendreau JF, et al. Efficacy of milnacipran in patients with fibromyalgia. J Rheumatol 2005; Oct;32(10):1975-85. PMID: 16206355.
7. Arnold LM, Hess EV, Hudson JI, et al. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. Am J Med 2002; Feb 15;112(3):191-7. PMID: 11893345.
8. Stening KD, Eriksson O, Henriksson KG, et al. Hormonal replacement therapy does not affect self-estimated pain or experimental pain responses in post-menopausal women suffering from fibromyalgia: a double-blind, randomized, placebo-controlled trial. Rheumatology (Oxford) 2011; Mar;50(3):544-51. PMID: 21078629.
9. Sadreddini S, Molaeefard M, Noshad H, et al. Efficacy of Raloxifen in treatment of fibromyalgia in menopausal women. Eur 2008; Jul;19(5):350-5. PMID: 18549938.
10. Assis MR, Silva LE, Alves AM, et al. A randomized controlled trial of deep water running: clinical effectiveness of aquatic exercise to treat fibromyalgia. Arthritis Rheum 2006; Feb 15;55(1):57-65. PMID: 16463414.
11. Gusi N, Parraca JA, Olivares PR, et al. Tilt vibratory exercise and the dynamic balance in fibromyalgia: A randomized controlled trial. Arthritis Care Res 2010; Aug;62(8):1072-8. PMID: 20235191.
12. Hakkinen K, Pakarinen A, Hannonen P, et al. Effects of strength training on muscle strength, cross-sectional area, maximal electromyographic activity, and serum hormones in premenopausal women with fibromyalgia. J Rheumatol 2002; Jun;29(6):1287-95. PMID: 12064848.
13. Senna MK, Sallam RA, Ashour HS, et al. Effect of weight reduction on the quality of life in obese patients with fibromyalgia syndrome: a randomized controlled trial. Clin Rheumatol 2012; Nov;31(11):1591-7. PMID: 22948223.
14. Valkeinen H, Alen M, Hakkinen A, et al. Effects of concurrent strength and endurance training on physical fitness and symptoms in postmenopausal women with fibromyalgia: a randomized controlled trial. Arch Phys Med Rehabil 2008; Sep;89(9):1660-6. PMID: 18675392.
15. Junghaenel DU, Schwartz JE, Broderick JE. Differential efficacy of written emotional disclosure for subgroups of fibromyalgia patients. Br J Health Psychol 2008; Feb;13(Pt 1):57-60. PMID: 18230233.
16. Scheidt CE, Waller E, Endorf K, et al. Is brief psychodynamic psychotherapy in primary fibromyalgia syndrome with concurrent depression an effective treatment? A randomized controlled trial. General Hospital Psychiatry 2013; Mar-Apr;35(2):160-7. PMID: 23218844.
17. Castel A, Cascon R, Padrol A, et al. Multicomponent cognitive-behavioral group therapy with hypnosis for the treatment of fibromyalgia: long-term outcome. J Pain 2012; Mar;13(3):255-65. PMID: 22285609.
18. Edinger JD, Wohlgemuth WK, Krystal AD, et al. Behavioral insomnia therapy for fibromyalgia patients: a randomized clinical trial. Arch Intern Med 2005; Nov 28;165(21):2527-35. PMID: 16314551.
19. Fontaine KR, Conn L, Clauw DJ. Effects of lifestyle physical activity on perceived symptoms and physical function in adults with fibromyalgia: results of a randomized trial. Arthritis Res Ther 2010; 12(2):R55. PMID: 20353551.

20. Lera S, Gelman SM, Lopez MJ, et al. Multidisciplinary treatment of fibromyalgia: does cognitive behavior therapy increase the response to treatment? J Psychosom Res 2009; Nov;67(5):433-41. PMID: 19837206.
21. Bennett R, Russell IJ, Choy E, et al. Evaluation of patient-rated stiffness associated with fibromyalgia: a post-hoc analysis of 4 pooled, randomized clinical trials of duloxetine. Clin Ther 2012; Apr;34(4):824-37. PMID: 22421576.
22. Chappell AS, Bradley LA, Wiltse C, et al. A six-month double-blind, placebo-controlled, randomized clinical trial of duloxetine for the treatment of fibromyalgia. Int J Gen Med 2008; 1:91-102. PMID: 20428412.
23. Bradley LA, Bennett R, Russell IJ, et al. Effect of duloxetine in patients with fibromyalgia: tiredness subgroups. Arthritis Res Ther 2010; 12(4):R141. PMID: 20630058.
24. Arnold LM, Hudson JI, Wang F, et al. Comparisons of the efficacy and safety of duloxetine for the treatment of fibromyalgia in patients with versus without major depressive disorder. Clin J Pain 2009; Jul-Aug;25(6):461-8. PMID: 19542792.
25. Arnold LM, Palmer RH, Hufford MR, et al. Effect of milnacipran on body weight in patients with fibromyalgia. International Journal of General Medicine 2012; 5:879-87. PMID: 2013287150.
26. Arnold LM, Gendreau RM, Palmer RH, et al. Efficacy and safety of milnacipran 100 mg/day in patients with fibromyalgia: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2010; Sep;62(9):2745-56. PMID: 20496365.
27. Mease PJ, Clauw DJ, Gendreau RM, et al. The efficacy and safety of milnacipran for treatment of fibromyalgia. a randomized, double-blind, placebo-controlled trial.[Erratum appears in J Rheumatol. 2009 Mar;36(3):661]. J Rheumatol 2009; Feb;36(2):398-409. PMID: 19132781.
28. Clauw DJ, Mease P, Palmer RH, et al. Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial.[Erratum appears in Clin Ther. 2009 Feb;31(2):446], [Erratum appears in Clin Ther. 2009 Jul;31(7):1617]. Clin Ther 2008; Nov;30(11):1988-2004. PMID: 19108787.
29. Geisser ME, Palmer RH, Gendreau RM, et al. A pooled analysis of two randomized, double-blind, placebo-controlled trials of milnacipran monotherapy in the treatment of fibromyalgia. Pain pract 2011; Mar-Apr;11(2):120-31. PMID: 20642487.
30. Arnold LM, Leon T, Whalen E, et al. Relationships among pain and depressive and anxiety symptoms in clinical trials of pregabalin in fibromyalgia. Psychosomatics 2010; Nov-Dec;51(6):489-97. PMID: 21051680.
31. Arnold LM, Russell IJ, Diri EW, et al. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. J Pain 2008; Sep;9(9):792-805. PMID: 18524684.
32. Mease PJ, Russell IJ, Arnold LM, et al. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. J Rheumatol 2008; Mar;35(3):502-14. PMID: 18278830.
33. Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005; Apr;52(4):1264-73. PMID: 15818684.
34. Bhadra P, Petersel D. Medical conditions in fibromyalgia patients and their relationship to pregabalin efficacy: pooled analysis of Phase III clinical trials. Expert Opinion on Pharmacotherapy 2010; Dec;11(17):2805-12. PMID: 21039311.
35. Pauer L, Danneskiold-Samsoe B, Jespersen A, et al. Pregabalin for management of fibromyalgia (FM): A 14-week randomized, double-blind, placebo-controlled, monotherapy trial (Study A0081100). Ann Rheum Dis 2008; 87(Suppl II):256. PMID.
36. Byon W, Ouellet D, Chew M, et al. Exposure-response analyses of the effects of pregabalin in patients with fibromyalgia using daily pain scores and patient global impression of change. J Clin Pharmacol 2010; Jul;50(7):803-15. PMID: 20357295.
37. Arnold LM, Palmer RH, Gendreau RM, et al. Relationships among pain, depressed mood, and global status in fibromyalgia patients: post hoc analyses of a randomized, placebo-controlled trial of milnacipran. Psychosomatics 2012; Jul-Aug;53(4):371-9. PMID: 22677218.
38. Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study. Pain Med 2009; May-Jun;10(4):663-72. PMID: 19453963.
39. Drexler AR, Mur EJ, Gunther VC. Efficacy of an EMG-biofeedback therapy in fibromyalgia patients. A comparative study of patients with and without abnormality in (MMPI) psychological scales. Clinical and Experimental Rheumatology 2002; September/October;20(5):677-82. PMID: 2002390664.

40. Joshi MN, Joshi R, Jain AP. Effect of amitriptyline vs. physiotherapy in management of fibromyalgia syndrome: What predicts a clinical benefit? Journal of Postgraduate Medicine 2009; Jul-Sep;55(3):185-9. PMID: 19884743.
41. Hakkinen A, Hakkinen K, Hannonen P, et al. Strength training induced adaptations in neuromuscular function of premenopausal women with fibromyalgia: comparison with healthy women. Ann Rheum Dis 2001; Jan;60(1):21-6. PMID: 11114277.
42. Fisher DJ, Copas AJ, Tierney JF, et al. A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners. J Clin Epidemiol 2011; Sep;64(9):949-67. PMID: 21411280.